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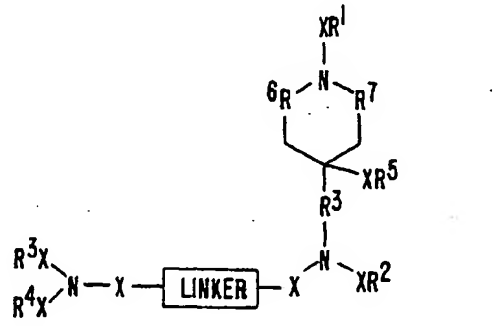
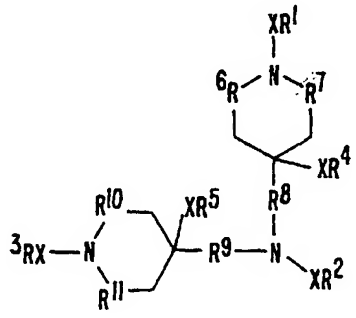
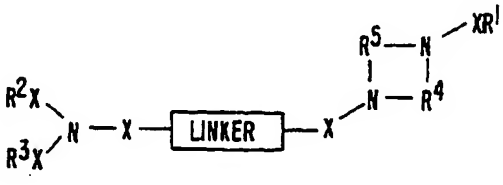
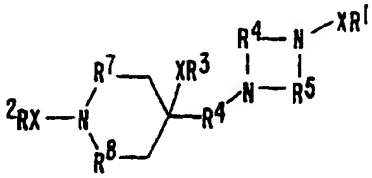
(54) Title: NON-QUINOLINE INHIBITORS OF MALARIA PARASITES









(57) Abstract: The present invention provides new compounds for inhibiting protozoal enzymes.

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NON-QUINOLINE INHIBITORS OF MALARIA PARASITES

BACKGROUND OF THE INVENTION

A number of serious diseases affecting humans, and domestic and livestock animals are caused by protozoal organisms such as, Kinetoplastida, Apicomplexa, Anaerobic protozoa, Microsporidia and Plasmodium, for example. The best known of these diseases is malaria.

Malaria is caused by organisms of the genus Plasmodium which infect and multiply within erythrocytes. Blood-stage infection is usually characterized by severe fever, sometimes accompanied by anemia, hypoglycemia, pulmonary edema, renal or hepatic failure, and coma which may occasionally prove fatal. Immunity may develop so as to reduce the severity of infection but takes many years and in individuals living in endemic areas complete elimination of parasites rarely occurs.

While the most serious form of malaria, caused by Plasmodium falciparum, is usually transmitted by a mosquito vector, it may also be transmitted by blood transfusion from asymptomatic donors. Almost all infected blood components, including red cells, platelet concentrates, white cells, cryoprecipitates and fresh plasma can transmit malaria. Malaria parasites can survive in red blood cells during cold storage for extended periods. The FDA's Blood Products Advisory Committee has issued recommendations for deferring blood donors at increased risk for malaria, however, these recommendations apply only to donations containing intact red blood cells. Donations used for preparing plasma, plasma components, or derivatives devoid of intact red blood cells are excluded from these regulations. Consequently, absolute safety from transfusion derived malaria is not insured. It is expected that increased immigration and travel from malaria endemic areas will intensify the risk of malaria through transfusion of red blood cell concentrates (RBCC) and platelet concentrates (PC).

The World Health Organization estimates that 280 million people are infected with malaria yearly (Gibbons, *Science,* **256**, 1135 (1992)). Although various classes of antimalarial agents exist, the most widely used are the quinoline-derived compounds. For example, chloroquine has been a particularly effective drug for both prophylaxis and therapy. The appearance of malaria strains which are resistant to

quinoline-derived drugs poses a threat to travelers and people in countries where malaria is endemic. Reports of multi-drug resistant strains of malaria parasites render the search for new antimalarial agents especially urgent.

The limitations of the current antiprotozoal chemotherapeutic arsenal underscore the need for new drugs, ideally directed against new targets. Quite surprisingly, the present invention provides such drugs.

SUMMARY OF THE INVENTION

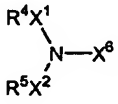
The present invention provides new drugs and methods of using these drugs to treat and prevent protozoal diseases in general, and malaria specifically.

In a first aspect, the present invention provides a novel genus of compounds having antiprotozoal activity. These compounds are particularly useful in interrupting the life cycle of plasmodia, such as *Plasmodium falciparum*, the causative agent of malaria.

In a first aspect, the present invention provides compounds having the general structure:

$$R^1—R^2—R^3. \qquad \text{(I)}$$

In Formula I, R^1 has a structure selected from Formulae II-IV, below:



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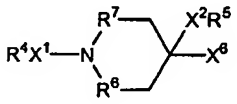

(III)

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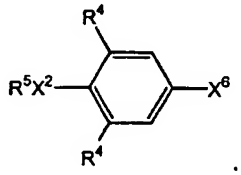
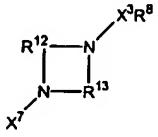


(IV)

R^2 is a member selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_1-C_{10} alkyl and substituted C_1-C_{10} alkyl; and R^3 is a member selected from



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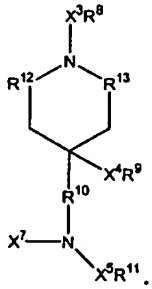


(V) (VI)

In each of Formulae II-VI, above X^1, X^2, X^3, X^4, X^5, X^6, and X^7 are members independently selected from a single bond, —O—, —C(O)—, —CO_2—, —C(O)NH—, —C(O)NR^{14}—, and —SO_2—; R^4, R^5, R^8, R^9 and R^{11} are members independently selected from H, —OH, alkoxy, C_1-C_{10} alkyl and C_1-C_{10} substituted alkyl; R^6, R^7, R^{10}, R^{12} and R^{13} are members independently selected from —C(O)—, —CO_2—, —C(O)NH—, —C(O)NR^{15}—, and —SO_2—; C_1-C_3 alkyl; and substituted C_1-C_3 alkyl; and R^{14}, R^{15}, R^{16} and R^{17} are members independently selected from alkyl, aryl, heteroaryl, carboxy ester, carboxamide, amino, N-acylamino, alkoxy, hydroxy, mercapto, phosphono and sulfono groups.

The advantages of these compounds and of the methods disclosed herein utilizing these compounds will be apparent from the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Presently preferred generic scaffolds for the compounds of the invention.

Figure 2 (A-B). A representative template for performing SAR at various regions of a scaffold of the invention and exemplary SAR at different the different regions of this template: (A) Representative template for optimizing SAR; (B) SAR in the R^2 region; (C) SAR in the linker region; (D) SAR in the R^1 region; (E) SAR in the R^3 region

Figure 3 (A-C). Exemplary compounds of the invention having various substitution patterns: (A) at the R^1 region; (B) at the R^3 region; (C) at the

Figure 4. An exemplary synthetic scheme leading to compound 7.

Figure 5. An exemplary synthetic scheme leading to compounds 6 and 8.

Figure 6. An exemplary synthetic scheme leading to compounds 9 and 10.

Figure 7. An exemplary synthetic scheme leading to compounds 14-21.

Figure 8. An exemplary synthetic scheme leading to compound 60.

Figure 9. An exemplary synthetic scheme leading to compounds 22-33.

Figure 10. An exemplary synthetic scheme leading to compounds 37-40.

Figure 11. An exemplary synthetic scheme leading to compounds 12-13 and 41-42.

Figure 12. An exemplary synthetic scheme for converting compound 55 to compounds 43 and 44.

Figure 13. An exemplary synthetic scheme for converting compound 69 to 45.

Figure 14 (A-B). An exemplary synthetic scheme for compounds 100 and 110.

Figure 15. An exemplary synthetic scheme for compounds 120 and 130.

Figure 16. An exemplary synthetic scheme for compounds 140 and 150.

Figure 17. Exemplary compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION AND THE PREFERRED EMBODIMENTS

A. Introduction

The present invention provides an array of novel compounds and libraries of these novel compounds. In preferred embodiments, these compounds act as inhibitors of protozoal enzymes and are useful pharmaceutical agents for treating and preventing protozoal infections. For clarity of presentation, the discussion that follows is principally focused on compounds of the invention that inhibit enzymes relevant to the organism *Plasmodium falciparum*, the causative agent of malaria. This focus is intended to be illustrative and not limiting. Those of skill in the art will recognize that there is a great deal of structural homology and substrate specificity and activity overlap between the enzymes of *P. falciparum* and other protozoa. Thus, the compounds of the invention are also applicable in methods of treating and preventing diseases caused by a wide range of protozoa.

B. Definitions

Unless otherwise specified, the terms used herein are assigned their art-accepted meanings. The definitions offered herein are intended to supplement, not supplant, the art-accepted definitions.

"Substituted," as used herein, generally refers to an alkyl or aryl group that is elaborated with one or more of a wide range of substituents. When "substituted" is used in conjunction with alkyl, the substituent(s) can be pendent from the alkyl group, can interrupt the alkyl group or the substituent(s) can be both pendent from, and interrupt, the alkyl group.

The term "independently selected" is used herein to indicate that the groups so described can be identical or different

The term "alkyl" is used herein to refer to a branched or unbranched, saturated or unsaturated, hydrocarbon radical having from 1-30 carbons and preferably, from 4-20 carbons and more preferably from 6-18 carbons. When the alkyl group has from 1-6 carbon atoms, it is referred to as a "lower alkyl." Suitable alkyl radicals include, for example, structures containing one or more methylene, methine and/or methyne groups. Branched structures have a branching motif similar to i-propyl, t-butyl, i-butyl, 2-ethylpropyl, *etc.* As used herein, the term encompasses "substituted alkyls."

"Substituted alkyl" refers to alkyl as just described including one or more functional groups such as lower alkyl, aryl, acyl, halogen (*i.e.*, alkylhalos, *e.g.*, CF_3), hydroxy, amino, alkoxy, alkylamino, acylamino, acyloxy, aryloxy, aryloxyalkyl, mercapto, heteroatoms, both saturated and unsaturated cyclic hydrocarbons, heterocycles and the like. These groups may be attached to any carbon of the alkyl moiety.

The term "aryl" is used herein to refer to an aromatic substituent which may be a single aromatic ring or multiple aromatic rings which are fused together, linked covalently, or linked to a common group such as a methylene or ethylene moiety. The common linking group may also be a carbonyl as in benzophenone. The aromatic ring(s) may include phenyl, napthyl, biphenyl, diphenylmethyl and benzophenone among others. The term "aryl" encompasses "arylalkyl."

The term "alkylarene" is used herein to refer to a subset of "aryl" in which the aryl group is substituted with an alkyl group as defined herein.

"Substituted aryl" refers to aryl as just described including one or more functional groups such as lower alkyl, acyl, halogen, alkylhalos (*e.g.* CF_3), hydroxy, amino, alkoxy, alkylamino, acylamino, acyloxy, mercapto and both saturated and unsaturated cyclic hydrocarbons which are fused to the aromatic ring(s), linked covalently or linked to a common group such as a methylene or ethylene moiety. The linking group may also be a carbonyl such as in cyclohexyl phenyl ketone. The term "substituted aryl" encompasses "substituted arylalkyl."

The term "acyl" is used to describe a ketone substituent, —C(O)R, wherein R is alkyl or substituted alkyl, aryl or substituted aryl as defined herein.

The term "halogen" is used herein to refer to fluorine, bromine, chlorine and iodine atoms.

The term "hydroxy" is used herein to refer to the group —OH.

The term "amino" is used to describe primary amines,—NRR', wherein R and R' are independently selected from H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclyl and substituted heterocyclyl as defined herein.

The term "alkoxy" is used herein to refer to the —OR group, wherein R is a lower alkyl, substituted lower alkyl, aryl, substituted aryl, arylalkyl or substituted arylalkyl wherein the alkyl, aryl, substituted aryl, arylalkyl and substituted arylalkyl groups are as described herein. Suitable alkoxy radicals include, for example, methoxy, ethoxy, phenoxy, substituted phenoxy, benzyloxy, phenethyloxy, t-butoxy, *etc.*

The term "unsaturated cyclic hydrocarbon" is used to describe a non-aromatic group with at least one double bond, such as cyclopentene, cyclohexene, *etc.* and substituted analogues thereof.

The term "heteroaryl" as used herein refers to aromatic rings in which one or more carbon atoms of the aromatic ring(s) are substituted by a heteroatom such as nitrogen, oxygen or sulfur. Heteroaryl refers to structures which may be a single aromatic ring, multiple aromatic ring(s), or one or more aromatic rings coupled to one or more non-aromatic ring(s). In structures having multiple rings, the rings can be fused together, linked covalently, or linked to a common group such as a methylene or ethylene moiety. The common linking group may also be a carbonyl as in phenyl pyridyl ketone. As used herein, rings such as thiophene, pyridine, isoxazole, phthalimide, pyrazole, indole, furan, *etc.* or benzo-fused analogues of these rings are defined by the term "heteroaryl."

"Alkylheteroaryl" defines a subset of "heteroaryl" substituted with an alkyl group, as defined herein.

"Substituted heteroaryl" refers to heteroaryl as just described wherein the heteroaryl nucleus is substituted with one or more functional groups such as lower alkyl, acyl, halogen, alkylhalos (*e.g.* CF_3), hydroxy, amino, alkoxy, alkylamino, acylamino, acyloxy, mercapto, *etc.* Thus, substituted analogues of heteroaromatic rings such as thiophene, pyridine, isoxazole, phthalimide, pyrazole, indole, furan, *etc.* or benzo-fused analogues of these rings are defined by the term "substituted heteroaryl."

The term "heterocyclic" is used herein to describe a saturated or unsaturated non-aromatic group having a single ring or multiple condensed rings from 1-12 carbon atoms and from 1-4 heteroatoms selected from nitrogen, sulfur or oxygen

within the ring. Such heterocycles are, for example, tetrahydrofuran, morpholine, piperidine, pyrrolidine, *etc.*

The term "substituted heterocyclic" as used herein describes a subset of "heterocyclic" wherein the heterocycle nucleus is substituted with one or more functional groups such as lower alkyl, acyl, halogen, alkylhalos (*e.g.* CF_3), hydroxy, amino, alkoxy, alkylamino, acylamino, acyloxy, mercapto, *etc.*

The term "alkylheterocyclyl" defines a subset of "heterocyclic" substituted with an alkyl group, as defined herein.

The term "substituted heterocyclicalkyl" defines a subset of "heterocyclic alkyl" wherein the heterocyclic nucleus is substituted with one or more functional groups such as lower alkyl, acyl, halogen, alkylhalos (*e.g.* CF_3), hydroxy, amino, alkoxy, alkylamino, acylamino, acyloxy, mercapto, *etc.*

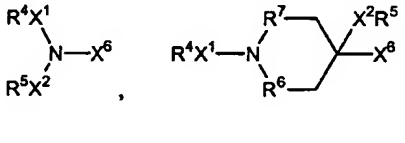
C. The Compounds

1. Structure

In a first aspect, the present invention provides compounds having the general structure:

$$R^1—R^2—R^3. \qquad \text{(I)}$$

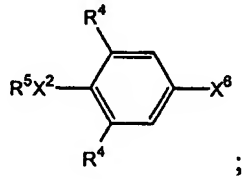
In Formula I, R^1 has a structure selected from Formulae II-IV, below:



(II)

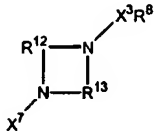
(III)

and



(IV)

R^2 is a member selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_1-C_{10} alkyl and substituted C_1-C_{10} alkyl; and R^3 is a member selected from



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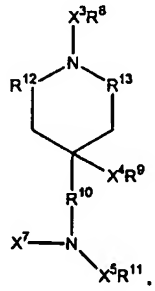
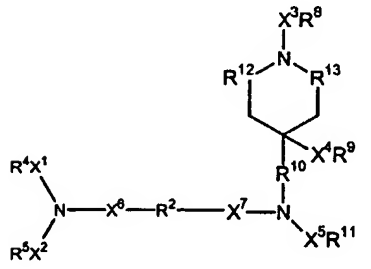


(VI)

In each of Formulae II-VI, above X^1, X^2, X^3, X^4, X^5, X^6, and X^7 are members independently selected from a single bond, —O—, —C(O)—, —CO_2—, —C(O)NH—, —C(O)NR^{14}—, and —SO_2—; R^4, R^5, R^8, R^9 and R^{11} are members independently selected from H, —OH, alkoxy, C_1-C_{10} alkyl and C_1-C_{10} substituted alkyl; R^6, R^7, R^{10}, R^{12} and R^{13} are members independently selected from —C(O)—, —CO_2—, —C(O)NH—, —C(O)NR^{15}—, and —SO_2—; C_1-C_3 alkyl; and substituted C_1-C_3 alkyl; and R^{14}, R^{15}, R^{16} and R^{17} are members independently selected from alkyl, aryl, heteroaryl, carboxy ester, carboxamide, amino, N-acylamino, alkoxy, hydroxy, mercapto, phosphono and sulfono groups.

In a presently preferred embodiment, a substituted alkyl moiety is selected from straight-chain, branched-chain or cyclic alkyl groups having from 1-10 carbon atoms. The carbon chain is optionally interrupted by from 1 to 5 heteroatoms. Preferred heteroatoms include, N, O, P and S. When more than one heteroatom is present, each heteroatom is selected independently of the others. In addition to, or instead of, the heteroatom substituents, the alkyl moiety can be substituted with other groups. Preferred groups include, alkyl, aryl, heteroaryl, carboxy ester, carboxamide, amino, N-acylamino, alkoxy, hydroxy, mercapto, phosphono, sulfono and the like.

In a preferred embodiment, the compounds have a structure according to Formulae VII-XI, below:



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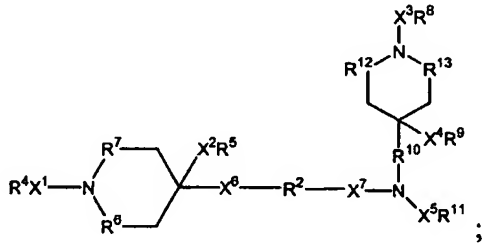

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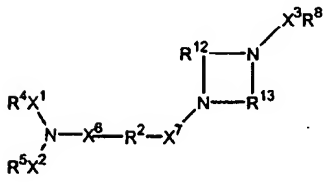

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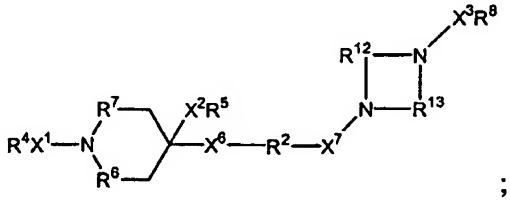

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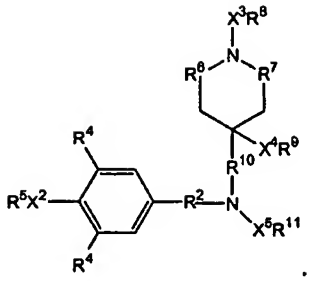
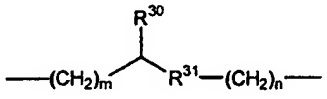


(XI)

In each of Formulae VII-XI, the groups X^{1-7} and R^{4-17} have the identities set forth in connection with Formulae II-VI, above.

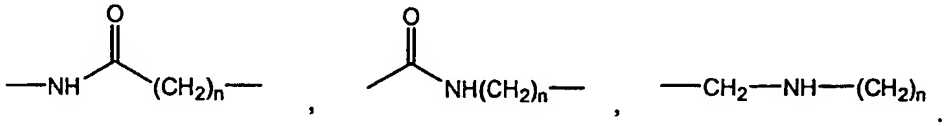
In another preferred embodiment, R^2 has a structure according to Formula XII:



(XII).

In Formula XII, R^{30} is a member selected from H and (=O), R^{31} is selected from —NH— and —O—; and m and n are numbers independently selected from 0 to 10, inclusive.

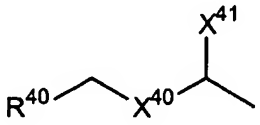
In a still further preferred embodiment, R^2 has a structure according to Formulae XIII-XV, below:



(XIII) (XIV) (XV)

In Formulae XIII- XV, n is an integer between 1 and 5, inclusive and more preferably, an integer between 2 and 4, inclusive.

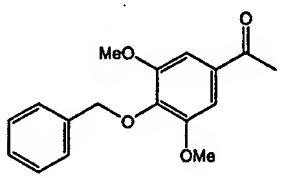
In another preferred embodiment, the compounds of the invention have a structure according to Formula I, in which R^1 has a structure according to Formula XVI, below:



(XVI).

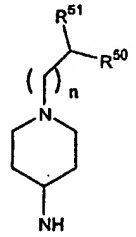
In Formula XVI, R^{40} is a member selected from benzene, substituted benzene, and polycyclic hydrocarbons; X^{40} is a member selected from —CH_2— and —O—; and X^{41} is a member selected from H and (C=O).

In a still further preferred embodiment, R^1 has a structure according to Formula XVII, below:



(XVII).

In other preferred embodiments, R^3 has a structure according to Formula XVIII, below:



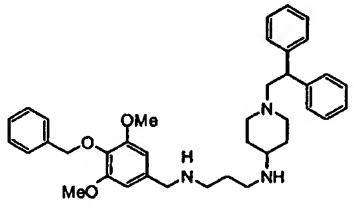
(XVIII).

In Formula XVIII, R^{50} and R^{51} are members independently selected from H, aryl, substituted aryl, heteroaryl and substituted heteroaryl groups; and n is a number from 0 to 5, inclusive.

In a still further preferred embodiment, R^{50} and R^{51} are both benzene.

Presently preferred compounds of the invention are displayed in Table 1.

Table 1



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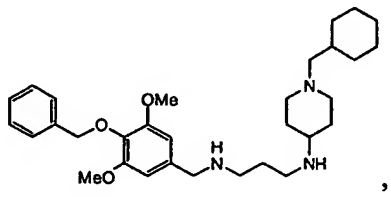

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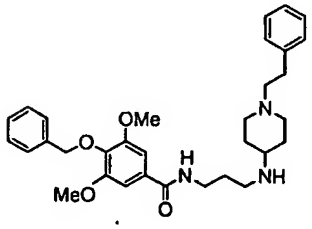

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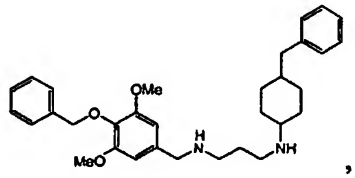

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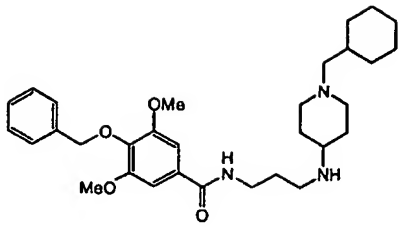
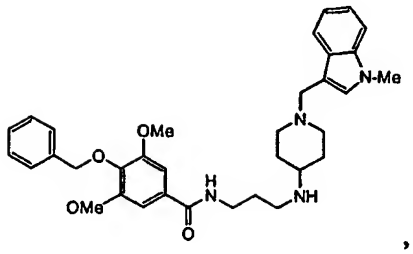

OMe
MeO
H
N
NH
O
N

,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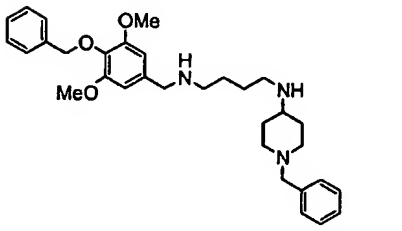
OMe
H
N
NH
O
N

,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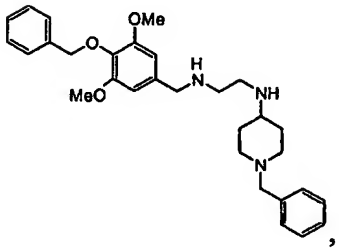
N
NH
N

,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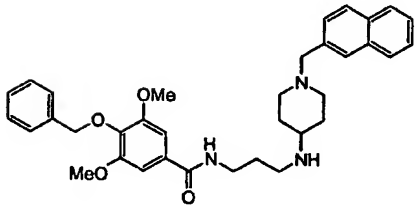
N
NH
N

,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O
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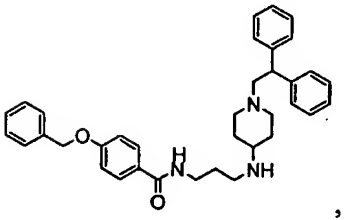
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NH
O
N

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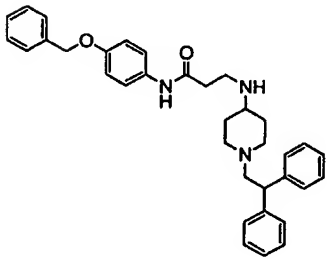
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H
NH
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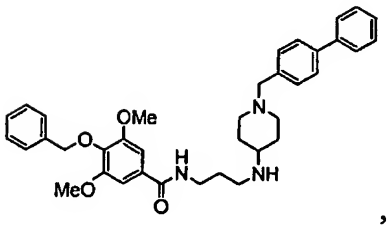
,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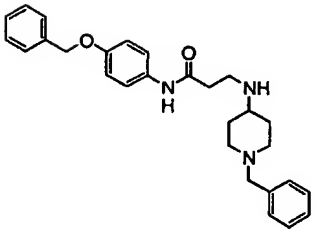
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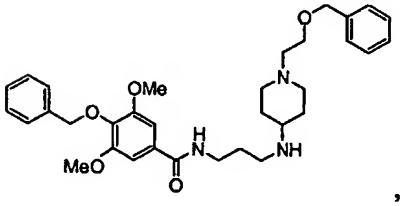
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NH
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N

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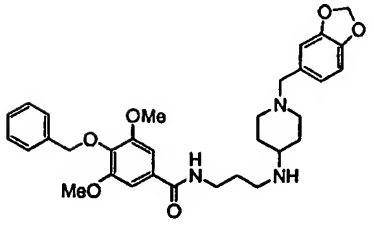
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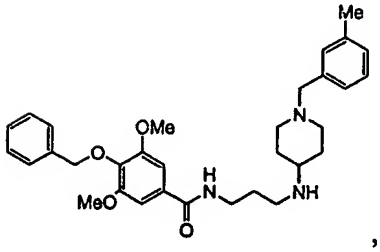
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MeO
H
N
NH
O
N

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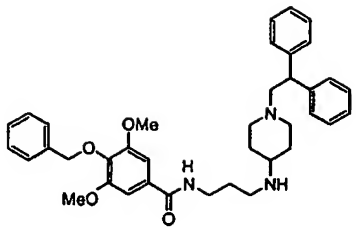
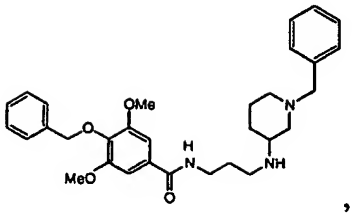
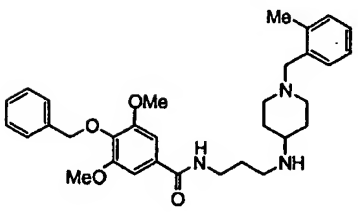
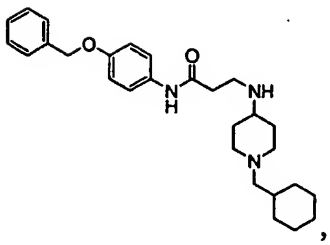
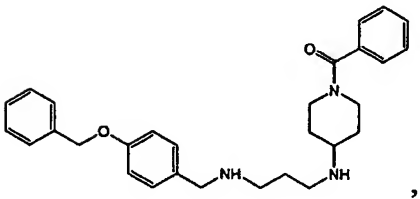
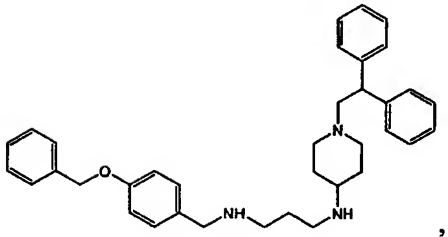
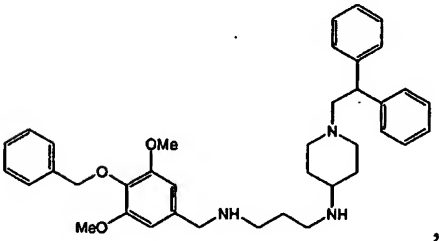
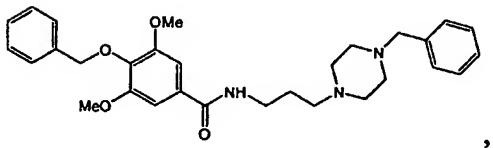
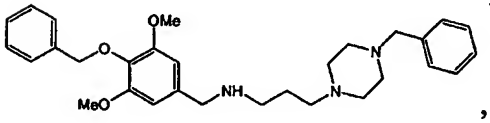
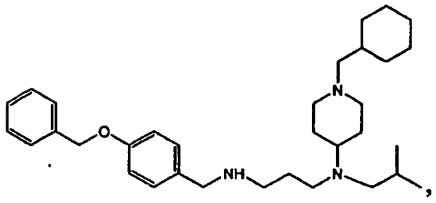
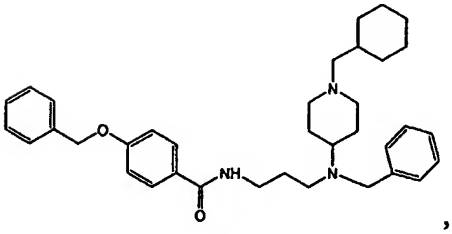
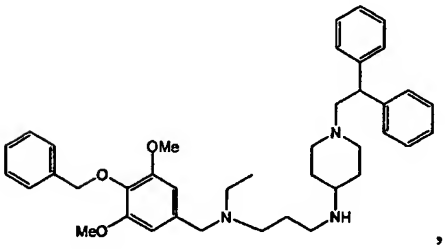
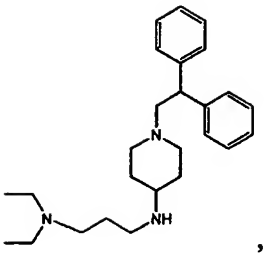
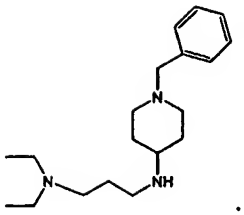

















2. Synthesis

In addition to the compounds of the invention, the present invention also provides methods for synthesizing these compounds. Representative examples of synthetic pathways leading to the compounds of the invention are set forth in **Figure 4** through **Figure 13**.

Figure 4 sets forth the synthesis of compound **7**, from 4-amino-1-benzylpiperidine using a multistep procedure. In step *a*, 4-amino-1-benzylpiperidine is alkylated using 1-bromo-3-chloropropane. In step *b*, the adduct of this reaction is amine-protected at the exocyclic amine by the action di-t-butyl dicarbonate. The amine-protected chloro derivative is then reacted with NaN_3, to replace the chloro group with an azido moiety in step *c*. The azide is reduced to the corresponding amine, in step *d*, by the action of $SnCl_2$. Following its isolation, the amine is coupled to 4-benzyloxy-3,5-dimethoxybenzoic acid, in step *e*. The t-Boc protected amine is subsequently deprotected, in step *f*, by the action of TFA. In step *g*, the amido carbonyl moiety is reduced by the action of $LiAlH_4$.

Figure 5 sets forth the synthesis of compounds **6** and **8**. These compounds vary in the number of carbon atoms included in the linker arm (R^2) portion. Substantially as described above, 4-amino-1-benzylpiperidine is alkylated, converted to the azide, amine protected, the azide is reduced, the resulting amine is coupled with 4-benzyloxy-3,5-dimethoxybenzoic acid, the t-Boc protect amine is deprotected and the amide carbony is reduced, thereby producing compounds **6** and **8**.

Figure 6 sets forth the synthesis of compounds **9** and **10**. In step *a*, 4-benzyloxy-3,5-dimethoxybenzyl alcohol is alkylated at the alcohol hydroxy with 4-(N-Boc-N'-3-chloropropyl)amino-1-benzylpiperidine. In step *b*, the t-Boc groups is removed, substantially as described above.

Figure 7 sets forth the synthesis of a library of compounds consisting of compounds **14-21**. The libraries are synthesized from amine precursors by coupling carboxylic acids to them using polymer-bound EDC.

Figure 8 sets forth the synthesis of compound **60** from compound **47**. In step *a*, compound **47** is reductively debenzylated using Pd/C and H_2. The piperidine secondary amine is amidated using allyl chloroformate in step *b*. The resulting compound is converted to the azide, the azide is reduced to the amine and the amine is acylated with 4-benzyloxy-3,5-dimethoxybenzoic acid substantially as described above. The allyl protected secondary amine is deprotected, in step *f*.

Figure 9 sets forth the preparation of a library of compounds of the invention consisting of compounds **22-33** from compound **60**. This library is prepared by reductively aminated using an array of aldehydes and sodium cyanoborohydride and purified using ion exchange.

Figure 10 sets forth the synthesis of compounds **37-40**. In step *a*, 4-benzyloxy-3,5-dimethoxybenzoic acid is aminated using an alkyldiamine. The resulting amine is treated with a keto-piperidine derivative in step *b* and the amide group of the resulting amide is reduced substantially as described above.

Figure 11 sets forth the synthesis of compounds **12-13** and **41-42**. Starting with 4-benzyloxyaniline, the aniline amine is converted to an amide using N-Boc-4-aminobutyric acid, in step *a*. In step *b*, the Boc group is removed and, in step *c*, the free amine is used to reductively aminate a keto-piperidine derivative.

Figure 12 sets forth the synthesis of compounds **43** and **44** from a common precursor, compound **55**. In this scheme, the piperidine secondary amine is protected, the chloro group is converted to an azide, which his reduced to an amine, the amine is used in a reductive amination and the Boc is removed substantially as described above.

Figure 13 sets for the deprotection, by removal of the Boc group of compound **60** to produce compound **45**.

Figure 14 (A) sets forth the synthesis of compound **100**. This scheme begins with the acylation of the secondary amine of a piperidine compound and the reduction of the resulting amide to the corresponding amine. The chloro group is converted to an azide, which his reduced to an amine, the amine is used in a reductive amination and the Boc is removed substantially as described above. (B) sets forth a substanially similarroute to compound **110**.

Figure 15 sets forth the synthesis of compounds **120** and **130** from a common precursor amine. The amine is used to reductively aminate a benzaldehyde derivative. Compound **120** is produced by simple Boc deprotection. Compound 130 is produced by a second reductive amination using acetaldehyde.

Figure 16 sets forth the synthesis of compounds **140** and **150** from a common precursor using methods described above.

The schemes described above are intended to be illustrative of methods and pathways that are of use in preparing the compounds of the invention. One of skill in the art, on reviewing these schemes, will find apparent many useful variations on these methods and pathways. Although not explicitly set forth herein, such variations are within the scope of the present invention.

d. Libraries

In addition to the individual compounds described herein, the present invention also provides a library comprising at least two compounds of the invention. Although the practical upper limit on the number of compounds contained in a library is dictated only by the complexity of the library constituents and the number of variable functionalities, in a preferred embodiment, the library comprises at least 5 compounds, preferably at least 50 compounds and more preferably at least 5000 compounds. The libraries of the invention can be selected using calculational structure-activity methods (I. D. Kuntz, *Science* **257**, 1078-1082 (1992).; I. D. Kuntz, *et al.*, *Accts. Chem. Res.* **27**, 117-123 (1994)) and prepared using combinatorial chemistry (L. A. Thompson, *et al.*, *Chem Rev.* **96**, 555-600 (1996); E. M. Gordon, *et al.*, *J. Med. Chem.* **37**, 1385-1401 (1994)) .

Structure-based design uses information gleaned from crystallographic and magnetic resonance experiments on a target macromolecule, frequently an enzyme, to guide the selection or design of inhibitors. Computation plays a major role in this endeavor (I. D. Kuntz, *et al.*, *Accts. Chem. Res.* **27**, 117-123 (1994); N. C. Cohen, *et al.*, *J. Med. Chem.* **33**, 883-894 (1990)). Combinatorial chemistry is based on general chemical transformations that allow different building blocks to be combined in high yield. These transformations can be performed in parallel to synthesize libraries of related compounds rapidly and efficiently (L. A. Thompson, *et al.*, *Chem Rev.* **96**, 555-600 (1996); E. M. Gordon, *et al.*, *J. Med. Chem.* **37**, 1385-1401 (1994)).

Nonetheless, the discovery of a new lead compound or the improvement of the properties of an existing lead are still demanding tasks.

Combinatorial approaches to ligand identification initially focused on biopolymer libraries prepared by either chemical or biological methods (M. A. Gallop, *et al., J. Med. Chem.* **37**, 1233-1251 (1994)). For these libraries, all possible combinations of the building blocks are typically used since there are only four natural nucleotide building blocks for aptamer libraries and 20 proteinogenic amino acid building blocks for peptide libraries. Both the structures of the compounds and the theoretical number of compounds in the library are determined by setting the length of the biopolymer chain. Recently, considerable efforts have been directed toward the preparation of libraries of compounds that encompass a wider spectrum of chemical transformations, leading to a broader range of properties than found in peptides or oligonucleotides (L. A. Thompson, *et al., Chem Rev.* **96**, 555-600 (1996); E. M. Gordon, *et al., J. Med. Chem.* **37**, 1385-1401 (1994)). These new approaches introduce significant challenges into library design.

An element of any library design is the procedure for selecting the compounds to synthesize. This includes the choice of the scaffold, the basic reactions and the nature of the building blocks. If the building blocks are readily available components such as amines, aldehydes or carboxylic acids, the number of potential compounds to be considered can be quite large. For example, combining three building blocks with thousands of components at each position leads to over 1 billion compounds. While different strategies have distinct practical limits, typically a researcher is prepared to synthesize only thousands of spatially separate compounds and tens of millions of compounds in mixtures. Furthermore, evaluation and deconvolution of a very large library become rate-limiting activities (N. K. Terrett, *et al., Bioorg. Med. Chem. Lett.* **5**, 917-922 (1995)). Thus, there would be significant advantages to a method of reducing the synthetic effort to a small subset of compounds biased towards the desired properties.

The standard strategies for reducing potential choices are diversity selection and directed selection. Diversity approaches attempt to maximize the sampling of chemical and biological properties given a fixed number of compounds (R. J. Simon, *et al., Proc. Natl. Acad. Sci. U.S.A.* **89**, 9367-9371 (1992)). In directed libraries the size, and often the diversity, of the library is reduced by selecting those building blocks that are predicted to have favorable interactions with the target, or by eliminating candidates that are *a priori* believed to have unfavorable interactions. A directed library can be based on substrate preferences, information about known inhibitors or, on an assessment of the

potential interaction of specific functional groups with the target. Both diverse and directed strategies permit a multistage attack with second libraries generated from active compounds found in the first round.

The development of general and efficient approaches to identify small, non-peptidic inhibitors of protozoal enzymes (*e.g.*, aspartic proteases) continues to be of interest because of their important roles in therapeutically relevant processes (K. Takahashi, Ed., *Aspartic Proteinases Structure, Function, Biology, and Biomedical Implications* (Plenum Press, New York, 1995); J. Adams, *et al.*, *Ann. Rep. Med. Chem.* 31, 279-288 (1996); J. J. Edmunds, *et al.*, *Ann. Rep. Med. Chem.* 31, 51-60 (1996); D. K. Miller, *Ann. Rep. Med. Chem.* 31, 249-268 (1996)).

Potent inhibitors of protozoal enzymes can be readily accessed by the incorporation of an isostere that mimics the geometry of the tetrahedral intermediate in place of the scissile bond of the peptide substrate. Unfortunately, these inhibitors have limited therapeutic utility due to the poor oral availability and/or short circulating half-lives that result from their peptidic nature. Non-peptidic inhibitors of protozoal enzymes exhibit more efficacious pharmacokinetic and pharmacodynamic profiles. Thus, the present invention will generally apply structure-based design and combinatorial chemistry techniques to develop non-peptide inhibitors of protozoal enzymes.

d. Compound activity

The compounds of the present invention are useful as inhibitors of enzymes that are implicated in the life cycle of protozoa. Preferred compounds of the invention have an activity towards one or more selected protozoal enzymes. This activity is preferably of sufficient magnitude to allow the compound to be used in the treatment and prevention of a disease caused by the protozoa. Moreover, compounds of the invention having sufficient activity can be used in biological and pharmacological assays and screening procedures involving the protozoa and/r the enzymes. As used herein, the term "inhibition" refers to both reduction and cessation of activity.

Details of the life cycle and pathogenicity of parasites are given in standard texts (*see*, for example, Schmidt *et al.* (1989) FOUNDATIONS OF PARASITOLOGY, Times Mirror/Mosby College Publishing, St Louis, U.S.A.; Urquhart *et al.* (1987) VETERINARY PARASITOLOGY, Longman Scientific and Technical, London, U.K.).

In a presently preferred embodiment, the invention provides a compound according to Formula I having an IC50 towards a protozoal enzyme of less than 5000 nanomolar, preferably less than 500 nanomolar, and more preferably less than 50 nanomolar. Even more preferred are compounds that have an IC50 of from about 0.05 nanomolar to about 40 nanomolar, and more preferably from about 1 nanomolar to about 20 nanomolar.

Proteases are normally divided into four main classes of serine, cysteine (thiol), aspartyl (carboxyl) and metallo-proteases. Proteases are involved in important physiological processes that range from protein catabolism or post-translational modification as found in lysosomal metabolism, to involvement in extracellular digestion of dietary proteins.

The compounds of the invention can be used to inhibit the activity of a range of protozoal enzymes. In a preferred embodiment, the enzyme is selected from cysteine protease, aspartyl protease and combinations thereof.

The enzymes inhibited by the compounds of the invention are components of essentially and known protozoal organism. In a preferred embodiment the enzyme comprises a component of an organism selected from Kinetoplastida, Apicomplexa, Anaerobic protozoa, Microsporidia and Plasmodium.

The present invention relates to the treatment and prophylaxis of protozoal infections caused by protozoa, including Kinetoplastida, Apicomplexa, Anaerobic protozoa, Microsporidia and Plasmodium. More particularly the invention is concerned with the use of compounds according to Formula I and physiologically acceptable salts and physiologically functional derivatives thereof.

Kinetoplastida include the Trypanosomes of which *Trypanosoma rhodiense*, *Trypanosoma gambiense* and *Trypanosoma cruzi* are of particular importance. *T. rhodiense* and *T. gambiense* cause sleeping sickness, which is fatal in humans unless treated. The trypanosome parasites live and multiply initially in the blood and tissue fluid of their host, producing a febrile condition which may be quite mild. After a few months (*T. rhodiense*) or a year or so (*T. gambiense*) the parasites invade the central nervous system and multiply in the cerebrospinal fluid, ultimately causing brain damage which leads to the coma from which the disease gets its name.

T. cruzi causes Chagas disease in humans. In children, the disease takes the form of an acute fever which can cause death. In adults, the infection is chronic, involves the heart or the alimentary tract and can be fatal.

The Kinetoplastida also include the genus Leishmania which cause leishmaniasis in humans. The parasites are also frequently found in dogs and rodents which may serve as reservoirs for the parasite. Leishmania parasites are ingested by the macrophage cells of their host, but instead of being destroyed the parasites thrive and multiply within the macrophages. In visceral leishmaniasis, caused by *L.donovani*, parasitized macrophages occur in all tissues, including the blood, and although the disease is slow, it is usually fatal unless treated. *L.tropica* causes cutaneous leishmaniasis in which the parasites are restricted to ulcers in the skin. In Brazil, *L-Braziliensis* causes mucocutaneous leishmaniasis which is a very severe disease; the mucous membranes of the nose, mouth and pharynx become infected and ultimately destroyed.

The Apicomplexa include the Babesia parasites which inhabit erythrocytes and which are of veterinary as well as medical importance. *B.divergens* is the European species that causes bovine babesiosis and, although not normally parasitic in man, it can cause a life threatening disease in splenectomized individuals, for which there is no recommended chemotherapy. The disease is usually associated with anemia, fever, enlargement of the spleen and, blocking of the capillaries in various tissues (including the brain), which may damage the cells by depleting their oxygen supply. The anemia may be accompanied by the lysis of erythrocytes and excretion of the released hemoglobin in the urine.

The Isospora are a genus of Apicomplexa which may infect humans and cause diarrhea. Another genus of Apicomplexa which may infect humans are the Sarcocystis which commonly infect herbivores. All species of Sarcocystis are almost entirely restricted to the muscle fibers of their host. If the infection is heavy, degeneration of the surrounding muscle fibers and consequent muscular weakness results along with some pain.

Parasitic anaerobic protozoa include species of Acanthanamoeba which normally inhabit soil and mud but which can cause throat infections in humans, particularly in infants.

Entamoeba histolytica is an anaerobic protozoan which normally inhabits the gut as a harmless commensal. Occasionally however, the parasites penetrate the mucosa and invade the sub-mucosa where they multiply to form a flask-shaped lesion or ulcer. Secondary bacterial infection of the ulcer may also occur. As the submucosa is eroded, many blood vessels are broken and bloody dysentery results. A common complication is the spread of amoebae via blood vessels to other organs, where they

invade and destroy the organ tissue and cause amoebic abscesses. The commonest site for development of such abscesses is the liver, because most of the blood from the gut is carried there by the hepatic portal system. Untreated amoebic dysentery may result in death from fluid and blood loss.

Giardia lamblia is a species of anaerobic protozoa which inhabits the small intestine of humans, monkeys and pigs. It is common in humans, especially in children, and can cause a disease called giardiasis or lambliasis. Heavy infections may cause acute diarrhea and epigastric pain. The parasites are thought sometimes to swim up the bile duct into the gall bladder where they may produce symptoms of jaundice, nausea and vomiting.

Trichomonas vaginalis is an anaerobic protozoan which inhabits the female vagina and the male urethra or prostrate and is common throughout the world, particularly in women. Most commonly, the parasite is non-pathogenic. However, the organism may be responsible for vaginal inflammation associated with a discharge in women and, more rarely, for inflammation of the urethra in males.

Infection by Microsporidia, such as *Enterocytozoon bieneuisi* or *Encephalitozoon cuniculi* causes an increase in the size of infected cells to such an extent that those cells cannot perform their natural function.

Encephalitozoon cuniculi can cause an encephalitis in humans in which the parasites are present in the cerebrospinal fluid.

Plasmodium cause a number of diseases, including malaria (*P. falciparum*). Upon infecting a host, the malaria parasite avidly consumes the host hemoglobin as its source of nutrients. Plasmepsin I and II are proteases from *Plasmodium falciparum* that are necessary during the initial stages of hemoglobin hydrolysis and digestion, which primarily occurs in the .alpha.chain, between Phe 33 and Leu 34, although other sites may serve as substrates for hydrolysis as well. It has been shown in cultures inhibition of plasmepsin by a peptidomimetic inhibitor is effective in preventing malarial hemoglobin degradation and in killing the parasite (Francis *et al.*, *EMBO J*, 13: 306-317 (1994)). Thus, persons of skill in the art expect inhibitors of *P. falciparum* enzymes to provide effective antimalarial therapy.

Patients in an already weakened state, such as children and the elderly, are particularly vulnerable to protozoal infections. Such infections can also be an extremely debilitating and complicating factor in immunocompromised patients (*i.e.* those with a defective or deficient immune system), who may be suffering from a number of different

infections. There is a variety of circumstances in which the immune system may be defective or deficient. Thus, for example immune system deficiency is common in immature or premature infants (neonates). It may also result from suppression by certain drugs, which may be deliberate e.g. in certain patients receiving organ transplants, or unavoidable *e.g.* as a side-effect of cancer chemotherapy. Disordered growth of one or more constituent parts of the immune system, *e.g.* as in certain forms of cancer, may also result in immunodeficiency. Immune deficiency may furthermore be caused by viral infections, including human immunodeficiency virus (HIV). Thus, in another embodiment, the compounds of the invention are used to treat infections in subjects that are immune compromised.

a. Measuring compound activity

The activity of the compounds described herein can be measured by any art-recognized method to acquire IC50 data from enzymes. Moreover, the activity of the compounds can be assessed by observing their effect on intact protozoa in culture.

In an exemplary screening procedure, library compounds are examined for inhibitory activity against aspartyl protease plasmepsin II in a high through-put fluorogenic assay. The enzyme activity is determined by observing an increase in fluorescence as the peptide substrate is cleaved by the enzyme. The substrate peptide is DABCYL-GABA-Glu-Arg-Nle-Leu-Phe-Ser-Phe-Pro-EDANS. Compounds are screened at 1 μM concentration in a 100 mM sodium acetate buffer (pH 5.0), containing 10% glycerol, and 0.01% Tween 20. Typical enzyme concentrations of approximately 2.5 nM and substrate concentrations of 1.25 μM are used. Compounds are added to the buffer as a dimethyl sulfoxide (DMSO) solution, resulting in a final DMSO concentration of 5%. Inhibition of enzyme activity by compounds is determined relative to "blank" wells containing buffer solution, enzyme, substrate, and DMSO without any inhibitory compound. Fluorescence activity was typically measured 3 times over 15 minutes after substrate addition to the enzyme/compound solution, using a 96-well fluorescence plate reader.

D. Pharmaceutical Compositions

In another embodiment, the invention provides a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a preferred embodiment, the pharmaceutical composition further comprises at least one additional antiprotozoal agent. The additional antiprotozoal agent is preferably active against a member selected from Kinetoplastida, Apicomplexa, Anaerobic protozoan, Microsporidia and Plasmodium. In certain preferred embodiments, the at least one additional antiprotozoal agent is active against a Plasmodium that causes malaria. Exemplary compounds include, artemether, arteether, artemisinine, dihydroartemisinine, artesunate, quinidine, mefloquine and combinations thereof.

Pharmaceutical formulations comprise the active ingredient (that is, the compound of Formula I or a physiologically acceptable salt or other physiologically functional derivative thereof) together with one or more pharmaceutically acceptable carriers thereof and optionally other therapeutic and/or prophylactic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formula and not deleterious to the recipient thereof.

The compound of Formula I or its salt or other physiologically functional derivative can conveniently be presented as a pharmaceutical formulation in unit dosage form. A convenient unit dose formulation preferably contains the active ingredient in an amount of from about 10 mg to about 3 g, more preferably from about 50 mg to about 1 g. An exemplary unit dose may contain for example 50 mg, 1 g, 2 g or 3 g of the active ingredient.

Pharmaceutical formulations include those suitable for oral, topical (including dermal, buccal and sublingual),rectal and parenteral (including subcutaneous, intradermal, intramuscular and intravenous), administration as well as administration by naso-gastric tube. The formulation may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration wherein the carrier is a solid are most preferably presented as unit dose formulations such as boluses, capsules or tablets each containing a predetermined amount of the active ingredient. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, lubricating agent, surface-active agent or

dispersing agent. Molded tablets may be made by molding an inert liquid diluent. Tablets may be optionally coated and, if uncoated, may optionally be scored. Capsules may be prepared by filling the active ingredient, either alone or in admixture with one or more accessory ingredients, into the capsule shells and then sealing them in the usual manner. Cachets are analogous to capsules wherein the active ingredient together with any accessory ingredient(s) is sealed in a rice paper envelope. The compound of Formula I or a physiologically acceptable salt or other physiologically functional derivative thereof may also be formulated as dispersible granules, which may for example be suspended in water before administration, or sprinkled on food. The granules may be packaged *e.g.* in a sachet. Formulations suitable for oral administration wherein the carrier is a liquid may be presented as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, or as an oil-in-water liquid emulsion.

Formulations for oral administration include controlled release dosage forms *e.g.* tablets wherein the active ingredient is formulated in an appropriate release-controlling matrix, or is coated with a suitable release-controlling film. Such formulations may be particularly convenient for prophylactic use.

The active ingredient may also be formulated as a solution or suspension suitable for administration via a nasogastric tube.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in molds.

Pharmaceutical formulations suitable for parenteral administration include sterile solutions or suspensions of the active compound in aqueous or oleaginous vehicles. Injectable preparations may be adapted for bolus injection or continuous infusion. Such preparations are conveniently presented in unit dose or multi-dose containers which are sealed after introduction of the formulation until required for use. Alternatively, the active ingredient may be in powder form which is constituted with a suitable vehicle, such as sterile, pyrogen-free water, before use.

The compound of Formula I or a physiologically acceptable salt or other physiologically functional derivative thereof may also be formulated as a long-acting depot preparation, which may be administered by intramuscular injection or by implantation e.g. subcutaneously or intramuscularly. Depot preparations may include, for

example, suitable polymeric or hydrophobic materials, or ion-exchange resins. Such long-acting formulations are particularly convenient for prophylactic use.

It should be understood that in addition to the aforementioned carrier ingredients the pharmaceutical formulations for the various routes of administration described above may include, as appropriate one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like, and substances included for the purpose of rendering the formulation isotonic with the blood of the intended recipient.

The compound of Formula I or a physiologically acceptable salt or other physiologically functional derivative thereof may also be used in accordance with the present invention in combination or concurrently with other therapeutic agents, for example agents used in the treatment of immunocompromised patients, including antibacterial agents; antifungal agents; anticancer agents such as interferons *e.g.* alpha-interferon; antiviral agents such as azidothymidine (AZT,zidovudine); immunostimulants and immunodulators. The compound of Formula I may also be administered in combination with a 4-pyridinol compound, as described in EPA 123,239 *e.g.* 3,5-dichloro-2,6-dimethylpyridinol (meticlorpindol). The compound of Formula I may also be administered in combination or concurrently with anti-diarrheal agents such as loperamide hydrochloride and/or diphenoxylate hydrochloride, or with morphine sulphate. Oral rehydration therapy may also be carried out concurrently.

Compositions suitable for veterinary use include those adapted for oral, parenteral, and intrarumenal administration.

Compounds suitable for oral administration include drenches (oral liquid dosing), which may be solutions or suspensions; tablets, boluses, pastes, or in-feed preparations in the form of powders, granules or pellets.

Alternatively, veterinary compositions may be adapted to be administered parenterally by subcutaneous, intramuscular or intravenous injection of a sterile solution or suspension, by implantation or as an intramammary injection whereby a suspension or solution is introduced into the udder via the teat.

E. Methods

In addition to the compounds and formulations of described herein, the present invention also provides various methods for using these compounds and formulations.

In another embodiment, the present invention provides a method for interrupting the reproductive cycle of a protozoan. The method includes: (a) contacting the protozoan with a compound according to Formula I, in an amount effective to interrupt said reproductive cycle.

In an additional embodiment, the present invention provides a method for inhibiting polymerization of heme caused by a protozoan. The method includes: (a) contacting the protozoan with a compound according to Formula I, in an amount effective to interrupt said reproductive cycle.

In a further embodiment, the invention provides a method for inhibiting a protozoal enzyme. The method includes: (a) contacting said enzyme with a compound according to Formula I, in an amount effective to inhibit said enzyme. Although any enzyme implicated in the life cycle of the protozoa can be inhibited using this method, in a preferred embodiment, the enzyme is a digestive enzyme of said protozoan. Even more preferably, the enzyme is a protease and it is a member selected from serine, cysteine, aspartyl, metalloproteases and combinations thereof.

In each of the above-described embodiment, the protozoa is preferably a member selected from Kinetoplastida, Apicomplexa, Anaerobic protozoan, Microsporidia and Plasmodium, and even more preferably, the protozoa is a causative agent of malaria.

Each of the above-described methods can be used either in vitro or in vivo. In a presently preferred embodiment, the method is used in vivo and it is a method of treating or preventing a protozoal infection in a subject. The method includes: (a) administering to the subject the pharmaceutical composition of the invention in an amount effective to treat or prevent said infection. In order for these compounds to be effective pharmaceutical agents, they should be of acceptable stability and toxicity and should have effective dosages that are conveniently obtainable.

a. Effective Dosages

Pharmaceutical compositions suitable for use in the methods of the invention include compositions wherein the active ingredient is contained in a

therapeutically effective amount, *i.e.*, in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, *inter alia*, on the condition being treated. For example, when administered in methods to eliminate malaria and/or delay the occurrence of a malaria recurrence, such compositions will contain an amount of active ingredient effective to achieve this result. Determination of an effective amount is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure herein.

For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target plasma concentrations will be those concentrations of active compound(s) that are capable of inducing inhibition of the target protozoal enzyme. In preferred embodiments, the enzyme activity is at least 25% inhibited. Target plasma concentrations of active compound(s) that are capable of inducing at least about 50%, 75%, or even 90% or higher inhibition of the enzyme are presently preferred. The percentage of inhibition of the enzyme channel in the patient can be monitored to assess the appropriateness of the plasma drug concentration achieved, and the dosage can be adjusted upwards or downwards to achieve the desired percentage of inhibition.

As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a circulating concentration that has been found to be effective in animals. A particularly useful animal model for sickle cell disease is a mouse malaria model. In a typical experiment, two cohorts of mice are infected with *P. falciparum*. One cohort receives the pharmaceutical formulation (*e.g.*, about three injections a day for about 4 days to about one week) and the other cohort (*i.e.*, the control group) is untreated. At the end of the treatment regimen, the efficacy of the compound and/or dosage level is evaluated by comparing parasitemia and survival of the two cohorts. Other models utilizing other protozoal infections can be utilized in a substantially similar manner.

Once an efficacious dosage has been determined in the animal model. A useful dosage can be calculated in humans. Upon administration in humans, the dosage can be adjusted by monitoring enzyme inhibition and adjusting the dosage upwards or downwards, as described above.

A therapeutically effective dose can also be determined from human data for compounds which are known to exhibit similar pharmacological activities. The

applied dose can be adjusted based on the relative bioavailability and potency of the administered compound as compared with the other compound.

Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods as are well-known in the art is well within the capabilities of the ordinarily skilled artisan.

In the case of local administration, the systemic circulating concentration of administered compound will not be of particular importance. In such instances, the compound is administered so as to achieve a concentration at the local area effective to achieve the intended result.

For use in the prophylaxis and/or treatment of protozoal infections, including both chronic infection and acute crisis, a circulating concentration of administered compound of about 0.001 μM to 20 μM is considered to be effective, with about 0.01 μM to 5 μM being preferred.

Patient doses for oral administration of the compounds described herein, which is the preferred mode of administration for prophylaxis and for treatment of chronic infection, typically range from about 1 mg/day to about 10,000 mg/day, more typically from about 10 mg/day to about 1,000 mg/day, and most typically from about 50 mg/day to about 500 mg/day. Stated in terms of patient body weight, typical dosages range from about 0.01 to about 150 mg/kg/day, more typically from about 0.1 to about 15 mg/kg/day, and most typically from about 1 to about 10 mg/kg/day.

For other modes of administration, dosage amount and interval can be adjusted individually to provide plasma levels of the administered compound effective for the particular clinical indication being treated. For example, if acute crises are the most dominant clinical manifestation, in one embodiment, a compound according to the invention can be administered in relatively high concentrations multiple times per day. Alternatively, if the patient exhibits only periodic crises on an infrequent, periodic or irregular basis, in one embodiment, it may be more desirable to administer a compound of the invention at minimal effective concentrations and to use a less frequent administration regimen. This will provide a therapeutic regimen that is commensurate with the severity of the individual's level of infection.

Utilizing the teachings provided herein, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial toxicity and yet is entirely effective to treat the clinical symptoms demonstrated by the particular

patient. This planning should involve the careful choice of active compound by considering factors such as compound potency, relative bioavailability, patient body weight, presence and severity of adverse side effects, preferred mode of administration and the toxicity profile of the selected agent.

b. Compound Toxicity

The ratio between toxicity and therapeutic effect for a particular compound is its therapeutic index and can be expressed as the ratio between LD_{50} (the amount of compound lethal in 50% of the population) and ED_{50} (the amount of compound effective in 50% of the population). Compounds that exhibit high therapeutic indices are presently preferred. Therapeutic index data obtained from cell culture assays and/or animal studies can be used in formulating a range of dosages for use in humans. The dosage of such compounds preferably lies within a range of plasma concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. See, *e.g.* Fingl *et al., In:* THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, Ch.1, p.1, 1975. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition and the particular method in which the compound is used.

c. Compound Stability

Another factor contributing to the pharmaceutical efficacy of the compounds of the invention is their stability under biologically relevant conditions. Compounds that are not rapidly degraded *in vivo* are expected to demonstrate better bioavailability and fewer side effects than analogous compounds that are rapidly degraded.

The stability of the compounds in various biological milieus can be assayed by methods known in the art. In one embodiment, the stability of the compounds is assayed in an *in vitro* preparation. In a preferred embodiment, the *in vitro* preparation is a liver microsome preparation. The results of such *in vitro* assays provide data relevant to the *in vivo* stability of the compounds of the invention. Other *in vitro* assays useful in assaying the stability of the compounds of the invention are known in the art.

In addition to *in vitro* methods, *in vivo* methods such as pharmacokinetic studies can be performed in a range of animal models. One or more compounds of the

invention can be administered to an animal, preferably a rat, at different dosages and/or by different routes (*e.g.*, i.v., i.p., p.o). Blood, urine and/or feces samples can be collected at serial time points and the samples assayed for the presence and/or concentration of the compound(s) of the invention and/or the metabolites of the compound(s).

Any appropriate quantity can be utilized to compare data from different compounds. Exemplary quantities include, half-life, bioavailability, amount of compound remaining intact after a predetermined time period and the like. In a preferred embodiment, the amount of compound remaining intact after a predetermined time period is utilized. As used herein, "intact" refers to compound that has not been metabolized or other wise degraded into a species different from the original compound.

In a preferred embodiment, the predetermined time period is from about two hours to about seventy-two hours, more preferably from about 4 hours to about twenty-four hours. In another preferred embodiment the amount of intact compound remaining after a predetermined time period of two hours is at least 40% of the initial dosage, preferably at least 50% and more preferably at least 70%.

Any technique that allows the detection and, preferably, the quantitation of the compound(s) and/or metabolites is appropriate for use in assaying the compounds of the invention. These methods include, but are not limited to, spectrometric methods (*e.g.*, NMR (*e.g.*, ^{19}F NMR), MS, IR, UV/vis), chromatographic methods (*e.g.*, LC, GC, HPLC) and hybrid methods utilizing both spectrometric and chromatographic methods (*e.g.*, GC/MS, LC/MS, LC/MS/MS). Further, the methods can utilize detectable labels such as compounds of the invention that are labeled with radioisotopes (*e.g.*, ^{3}H, ^{15}N, ^{14}C) or fluorescent labels (*e.g.*, fluorescein, rhodamine). Other methods for assaying the *in vivo* persistence of small organic molecules, particularly those applicable to bioactive molecules, will be apparent to those of skill in the art.

d. Multidrug Combinations

As discussed above, the present invention provides "cocktails" including one or more of the compounds of the invention and, generally, one or more known anti protozoal agents. Using such multidrug cocktails, it is often possible to combat drug resistant forms of the protozoa. Thus, the invention also provides for methods as discussed above in which a multidrug "cocktail" is utilized.

The following discussion focuses on the use of "cocktails" to combat Plasmodium. This focus is for clarity of presentation only, and it is to be understood that

the methods discussed below, or variations thereon, are applicable to other infective protozoal agents.

1. Blood Schizontocidal Activity

The initial evaluation of blood schizontocidal activity is carried out using the "4 day suppressive test" (*see, Ann. Trop. Med. Parasit.*, **64**: 41-51 (1970)). A battery of strains of rodent malaria, comprised of a range of drug-sensitive and drug-resistant lines of *Plasmodium berghei* and *P. yoelii*, is maintained for this purpose. The compounds are tested initially against drug-sensitive *P. berghei* N and P. y. nigeriensis NIG strain together with chloroquine-resistant *P. yoelii* sp NS strain. These strains of *P. yoelii* are incorporated into the preliminary screen because they have been found to be a far better model for *P. falciparum* than *P. berghei*. **P. berghei** N strain is also included since most of the lines resistant to standard antimalarials, which have been developed over the years, have this as their parent strain. Compounds which show activity in these preliminary tests are further tested against a range of resistant lines and tested for curative action.

2. Hosts and Parasites

(i). Vertebrate Host.

Random bred Swiss albino mice (TFW strain, supplied by A. Tuck and Son, Rayleigh, Essex) free of *Eperythrozoon coccoides* weighing between 18 and 20 grams are used for all of the tests. It is important that mice are free of *E. coccoides* and if there is any evidence of these organisms being present, treatment with either neoarsphenamine benzoate or tetracycline is commenced immediately.

(ii). Parasite Species and Strains

P. berghei

N(=Keyberg 173): Sensitive to all standard antimalarial drugs. Does not product gametocytes. Maintained by syringe passage;

ANKA: Sensitive to all standard antimalarials. Maintained by cyclical passage through *A. stephensi*.

P--derived from N: Highly resistant to primaquine. Maintained by syringe passage under primaquine pressure (60 mg/kg/day s.c.);

B--derived from N: Highly resistant to cycloguanil. Maintained by syringe passage under cycloguanil pressure (60 mg/kg/day s.c.);

PYR--derived from NK 65: Highly resistant to pyrimethamine. Maintained by syringe passage under pyrimethamine pressure (100 mg/kg/i.p. x 1);

ORA--derived from NK 65: Highly resistant to sulfonamides. Maintained by syringe passage under sulfaphenazole pressure (1000 mg/s.c x1);

Q--derived from N: Highly resistant to quinine. Maintained by syringe passage under drug pressure (600 mg/kg quinine hydrochloride po x 1).

P. yoelii

P. yoelii nigeriensis (N67; NIG)--Maintained by syringe passage or cyclical transmission through A. stephensi (Beech strain) without drug pressure. Used as a model for chloroquine-sensitive *P. falciparum* for causal prophylaxis studies;

P. yoelii ssp. NS--Moderately resistant to chloroquine. Maintained by cyclical passage through Anopheles stephensi and under drug pressure in mice (60 mg/kg s.c. x 1 at passage.);

MEF (=NS1100)--derived from NS: Highly resistant to mefloquine. Maintained by syringe passage under drug pressure (60 mg/kg s.c. x 1 at passage);

SH--derived from NS: Highly resistant to halofantrine. Maintained by syringe passage under drug pressure (30 mg/kg s.c. x 1 at passage);

ART--derived from NS: Highly resistant to artemisinin. Maintained by syringe passage under drug pressure (100 mg/kg s.c. x 1 at passage);

SPN--derived from NS: Highly resistant to pyronaridine. aintained by syringe passage under drug pressure (10 mg/kg sc x 1 at passage);

SAM--derived from NS: Highly resistant to amodiaquine Maintained by syringe passage under drug pressure (100 mg/kg sc x 1 at passage).

P. vinckei petteri

PET--Sensitive to all standard antimalarials. Syringe passaged, synchronous strain;

3. Protocols

Male, random-bred Swiss albino mice weighing 18-22 grams are inoculated intravenously with 10^7 parasitized red blood cells of the above strains.

Animals are then dosed once daily for four consecutive days beginning on the day of infection. Compounds are dissolved or suspended, using ultrasonication, where necessary to achieve an even suspension, in sterile distilled water with Tween 80 and administered subcutaneously, intraperitioneally, orally or by such other route as may be required

Where exceptional difficulty is encountered in preparing an aqueous preparation, the test compound is first dissolved in dimethyl sulfoxide and subsequently aqueous dilutions are prepared for use. he total amount of compound required is 250-1500 mg depending on active dose level found in preliminary screen. The parasitaemia is determined on the day following the last treatment and the ED..50 and ED.90 (*i.e.* 50% and 90% suppression of parasites when compared with untreated controls), estimated from a plot of log dose against activity. Standard error is calculated with the aid of Table 48, Geigy Scientific Tables, 6th Edition. The degree of cross resistance is determined by comparing activity in the sensitive and resistant strains.

4. Drug Interaction Studies

The use of combinations of two or more compounds provides a means of protecting the individual components of the mixture from the development of resistance as well as being an efficient form of therapy. In addition, the potential exists for reversing drug-resistance by combining an appropriate compound with the antimalarial to which resistance has been developed. New and better combinations can protect recently developed antimalarials from sharing the fate of most of the previous generation of drugs.

The "4-day test" technique has proved itself to be a sensitive system for detecting interactions between drugs. If two compounds are simultaneously administered in an appropriate series of dilutions then it is possible to determine the influence of one compound upon the ED90 of the other in a series or ratios of combination. The ED90 values obtained with combinations in a test of this type may be compared with those of the individual compounds to obtain an isobolar equivalent. These are plotted for each compound in an isobologram in order to demonstrate the presence of synergism, antagonism or a simple additive action.

The compounds, compositions and methods of the present invention are further illustrated by the examples that follow. These examples are offered to illustrate, but not to limit the claimed invention.

EXAMPLES

The Examples below, illustrate the synthesis of representative compounds of the invention.

General Methods.

In each of the Examples set forth below, certain general methods were practiced. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Anhydrous N,N-dimethylformamide (DMF) was purchased from Aldrich. Tetrahydrofuran (THF) was distilled under N_2 from sodium/benzophenone immediately prior to use. It was not necessary to use distilled solvents for rinsing of resin. Flash column chromatography was carried out using Merck 60 230-400-mesh silica gel. Thin layer chromatography (TLC) analyses were performed with Uniplate 250 μm silica gel plates from Analtech, Newark, DE (catalog no. 21521). ^{1}H NMR spectra were obtained with a UCB Bruker AM-400 FT spectrometer. Chemical shifts are reported in ppm. Coupling constants are reported in Hz. Unless otherwise noted, spectra were obtained in $CDCl_3$ with residual $CHCl_3$ as an internal standard at 7.25 ppm; spectra obtained in CD_3OD were referenced to the residual CD_3OH at 3.31 ppm. Elemental analyses were performed by M-H-W Labs, Phoenix, AZ.
Chloromethylpolystyrene (1% cross-linked) resin was obtained from Novabiochem, catalog no. 01-64-0002, 200-400 mesh size.

EXAMPLE 1

In this example, compound **46** is converted to compound **7**, via a multiple step synthesis. The synthetic steps in this Example are referenced to Scheme 1 set forth in **Figure 4**.

a. Alkylation of 4-amino-1-benzylpiperidine

To a solution of 1-bromo-3-chloropropane (1.0 g, 6.35 mmol) in CH_3CN (5 mL) was added 4-amino-1-benzylpiperidine (3.6 g, 19.5 mmol). The reaction mixture was stirred at room temperature for 16h. As the reaction proceeded, formation of a white precipitate was observed. The reaction mixture was treated with saturated $NaHCO_3$ (15 mL) to make the solution basic (pH ~9) and extracted with EtOAc (3×30 mL). The combined organic phase was dried over Na_2SO_4 and concentrated to afford a yellowish

solid. Silica gel column chromatography using 19:1 CH_2Cl_2/MeOH afforded 1.64 g of a pale yellowish solidified product (97%): ^{1}H NMR ($CDCl_3$) δ 1.25 (bs, 1H), 1.38 (ddd, J=4.0 Hz, J=16.2 Hz, J=18.7 Hz, 2H), 1.85 (td, J=3.2 Hz, J=12.4 Hz, 2H), 1.92 (quintet, J=6.8 Hz, 2H), 2.02 (dt, J=2.4 Hz, J=11.6 Hz, 2H), 2.45 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.77 (t, J=6.8 Hz, 2H), 2.84 (td, J=3.2 Hz, J=12.4 Hz, 2H), 3.50 (s, 2H), 3.62 (t, J=6.4 Hz, 2H), 7.28-7.36 (m, 4H), 7.21-7.17 (m, 1H).

b. Protection of the exocyclic amine

Di-t-butyl dicarbonate (1.52 g, 6.98 mmol) was added to a solution of **46** (1.55 g, 5.82 mmol) in THF (5 mL) and the reaction mixture was stirred at room temperature for 2h. The reaction mixture was concentrated and purified by silica gel column chromatography using 99:1 CH_2Cl_2/MeOH to afford 2.0g of a yellowish solidified product **47** (94%); ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.62-1.68 (m, 2H), 1.69-1.80 (m, 2H), 1.94-2.10 (m, 4H), 2.94 (d, 2H), 3.20-3.30 (m, 2H), 3.50 (s, 2H), 3.53 (t, J=6.4 Hz, 2H), 4.00 (bs, 1H), 7.25-7.28 (m, 1H), 7.31-7.35 (m, 4H).

c. Addition of azide

To a solution of **47** (1.92 g, 5.24 mmol) in DMF (5 mL) were added NaN_3 (3.41 g, 52.4 mmol) and NaI (0.79 g, 5.24 mmol) and the reaction mixture was stirred at 75-80 °C for 15h. The solvent was removed *in vacuo* and the resultant residue was diluted with $CHCl_3$ (20 mL). The organic phase was washed with water (2×20 mL), dried over Na_2SO_4, and then concentrated. Silica gel column chromatography using 49:1 CH_2Cl_2/MeOH afforded a 1.84 g of **48** as a colorless oil (94%); ^{1}H NMR ($CDCl_3$) δ 1.45 (S, 9H), 1.56-1.72 (M, 4H), 1.76 (quintet, 2H), 2.00 (t, 2H), 2.91 (d, 2H), 3.09-3.18 (m, 2H), 3.28 (t, 2H), 3.45 (s, 2H), 7.20-7.28 (m, 1H), 7.29-7.32 (m, 4H).

d. Reduction of azide to amine

To a solution of $SnCl_2$ (76 mg, 0.40 mmol) in THF (3 mL) were added PhSH (0.18 g, 1.61 mmol) and Et_3N (0.20 g, 2.01 mmol). The mixture was added to a solution of **48** (0.10 g, 0.27 mmol) in THF (2 mL) and the reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated and the residue was diluted with CH_2Cl_2 (5 mL) and then 2N NaOH (5 mL) was added to the solution. The aqueous phase was separated and extracted with with CH_2Cl_2 (2×10 mL). The combined organic

phase was dried over Na_2SO_4 and concentrated to provide 87 mg of a colorless oil (93 %); ^1H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.54-1.80 (m, 4H), 1.91-2.04 (m, 2H), 2.10-2.18 (bs, 2H), 2.68 (t, J=6.8 Hz, 2H), 2.92 (d, J=11.6 Hz, 2H), 3.05-3.28 (m, 2H), 3.47 (s, 2H), 7.20-7.26 (m, 1H), 7.28-7.31 (m, 4H).

e. Acylation of compound 49

A pre-mixed solution of 4-benzyloxy-3,5-dimethoxybenzoic acid (93 mg, 0.32 mmol), PyBOP (0.17 g, 0.32 mmol), HOAt (44 mg, 0.32 mmol) and DIPEA (87 mg, 0.67 mmol) in DMF (3 mL) was added to a solution of **49** in DMF (1 mL). The reaction mixture was stirred at room temperature for 16h under N_2 and DMF was removed *in vacuo*. The residue was diluted with $CHCl_3$ (10 mL) and the solution was washed with saturated $NaHCO_3$ (2×5 mL), then water (1×5 mL). The organic phase was dried over Na_2SO_4 and concentrated. Silica gel column chromatography using 97:3 CH_2Cl_2/ MeOH afforded 0.15 g of **50** as a colorless oil (88%); ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.64-1.85 (m, 6H, 2.00 (t, J=11.2 Hz, 2H), 2.95 (d, J=11.2 Hz, 2H), 3.32-3.45 (m, 4H), 3.49 (s, 2H), 3.58-3.71 (m, 1H), 3.88 (s, 6H), 5.05 (s, 2H), 7.15-7.36 (m, 10H), 7.45-7.51 (m, 2H), 8.20 (bs, 1H).

f. Deprotection of compound 50

Compound **50** (0.78 g, 1.26 mmol) was treated with 20% TFA in CH_2Cl_2 (10 mL) and stirred for 2h at 0 °C, then additional 2h at room temperature. The reaction mixture concentrated and the residual TFA was removed by adding toluene to form an azeotrope. Silica gel column chromatography using 45:5:1 CH_2Cl_2/MeOH/NH_4OH provided 0.70 g of **1** as a colorless oil (94%). The compound was dissolved in MeOH (2 mL) and the solution was acidified by adding 1M HCl/ether. The solution was concentrated to afford pure **1** in a salt form.

g. Reduction of benzylamide (1) to benzylamine (7)

Compound 1 (0.10 g, 0.17 mmol) was dissolved in THF (5 mL) and the solution was cooled down to 0 °C. $LiAlH_4$ (20 mg, 0.51 mmol) was added to the mixture at 0 °C and the reaction mixture was heated at reflux for 8h. The reaction mixture was cooled down to 0 °C and saturated Na_2SO_4 was added dropwise with stirring. The mixture was dried over $MgSO_4$ and the precipitate was filtered off. The filtrate was

concentrated and the resulting residue was purified using silica gel column chromatography with 45:5:1 CH_2Cl_2/MeOH/NH_4OH to afford 55 mg of a colorless oil (64%). The amine product was converted into a salt form by treating 1M HCl/ether in MeOH solution.

EXAMPLE 2

This Example describes the synthesis of compounds 6 and 8 using a multistep procedure. The synthetic steps in this Example are referenced to Scheme 2 set forth in **Figure 5**.

a. Azidoalkylation of 4-amino-1-benzylpiperidine and protection of the product

To a solution of 1-bromo-2-chloroethane (or 1-bromo-4-chlorobutane) (1 eq.) in DMF was added NaN_3 (1eq.) and the mixture was stirred at 75 °C for 24 h. The reaction mixture was then treated with 4-amino-1-benzylpiperidine (3eq.) and NaI (1eq.) and heated to 70 °C. After another 12h, the reaction mixture was concentrated *in vacuo* and the residue was treated with saturated $NaHCO_3$. The aqueous solution was extracted with EtOAc (3×) and the combined organic phase was dried over Na_2SO_4, then concentrated. The resultant crude compound was dissolved in THF and treated with Boc_2O (1.5 eq.). The reaction mixture was stirred at room temperature for 3h and concentrated. Silica gel column chromatography using 49:1 CH_2Cl_2/MeOH afforded a pure product.

b. Reduction of azide to amine

To a solution of $SnCl_2$ (1.5 eq.) in THF were added PhSH (6 eq.) and Et_3N (7.5 eq.). The mixture was then added into a solution of the azide derivative (1 eq.) in THF and the reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated and *in vacuo* and the residue was treated with CH_2Cl_2: 2N NaOH (v/v, 1:1). The aqueous phase was separated and re-extracted with CH_2Cl_2 (2×). The combined organic solution was dried over Na_2SO_4 and concentrated to provide an amine.

c. Acylation of amine

4-Benzyloxy-3,5-dimethoxybenzoic acid (1.2 eq.) was dissolved in DMF and HATU (1.2 eq.) was added to the solution followed by DIPEA (2.5 eq.). The pre-

mixed acid solution was added to an amine (1.0 eq.) in DMF and the reactioon mixture was stirred at room temperature for 16 h under N_2. The solvent was then removed *in vacuo* and the residue was diluted with $CHCl_3$. The organic solution was washed with saturated $NaHCO_3$ followed by water. The organic phase was dried over Na_2SO_4 and concentrated. Purification of the crude product by silica gel column chromatography using 19:1 CH_2Cl_2/MeOH afforded a pure compound.

d. Deprotection of the exocyclic amine

To a Boc-protected precursor was added 4N HCl in dioxane at 0 °C and the solution was stirred for 30 min. and then at room temperature for additional 1.5 h. The solvent was removed *in vacuo* and the resultant precipitate was purified by silica gel column chromatography using 45:5:1 CH_2Cl_2/MeOH/NH_4OH.

e. Reduction of benzylamide to benzylamine

The amide was reduced to amine according to the procedure described previously (*see*, Example 1, part *g*).

EXAMPLE 3

This Example describes the synthesis of compounds 9 and 10 by a multistep process. The synthetic steps in this Example are referenced to Scheme 3 set forth in **Figure 6**.

a. Alkylation of benzylic alcohol (51, 52)

4-Benzyloxy-3,5-dimethoxybenzyl alcohol (**51**) (0.12 g, 0.44 mmol) was added to the suspension of 60% NaH (20 mg, 0.48 mmol) in DMF (2 mL) under N_2. The mixture was stirred at room temperature for 4h and 4-(N-Boc-N'-3-chloropropyl)amino-1-benzylpiperidine (80 mg, 0.22 mmol) in DMF (1 mL) was added. The reaction mixture was stirred at room temperature for 48 h and concentrated *in vacuo*. Silica gel column chromatography of the residue using 19:1 CH_2Cl_2/EtOAc afforded 89 mg of **53** as a colorless oil (68%); ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H), 1.60-1.70 (m, 2H); 1.71-1.81 (m, 2H), 1.82-1.91 (m, 2H), 1.98-2.10 (m, 2H), 2.94 (d, J=11.2 Hz, 2H), 3.14-3.28 (m, 2H), 3.41-3.55 (m, 4H), 3.84 (s, 6H), 4.43 (s, 2H), 5.01 (s, 2H), 6.57 (s, 2H), 7.21-7.40 (m, 8H), 7.51 (d, J=6.8 Hz, 2H).

Compound **54** was prepared following the same procedure in 42% yield; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.58-1.90 (m, 6H), 1.92-2.08 (m, 2H), 2.96 (d, J=12.4 Hz, 2H), 3.12-3.23 (m, 2H), 3.45 (t, J=5.6 Hz, 2H), 3.50 (s, 2H), 4.42 (s, 2H), 5.07 (s, 2H), 6.97 (d, J=8.8 Hz, 2H), 7.27 (d, J=8.8 HZ, 2H), 7.29-7.38 (m, 8H), 7.41-7.43 (m, 2H).

b. Deprotection of exocyclic amine

The Boc-group was removed following the procedure described previously (**9**, X=OMe: 73%, **10**, X=H: 78%), *see*, Example 2, part *d*.

EXAMPLE 4

This Example describes the general procedures used to assemble libraries of the compounds of the invention based on the scaffold of compound **49**. The library assembly steps described herein are referenced to Scheme 4 set forth in **Figure 7**.

Polymer bound EDC (0.71 mmol/g, 0.30 g) was added to the solution of an acid (0.086 mmol) in $CHCl_3$ (2 mL) in a screw cap vial and stirred for 5 min. A solution of the amine (0.029 mmol) in $CHCl_3$ (1 mL) was then added to the suspension of the resin and the mixture was shaken for 6h at room temperature. The mixture was filtered using a polystyrene cartridge with 70 μm PE frits attached to a Teflon stopcock for the work-up process. The resin was washed with $CHCl_3$ (3×1 mL). Approximately 0.3 g of an ion exchange resin was added to the filtrate and the mixture was shaken for an additional 5h. The mixture was transferred into a cartridge and the resin was washed with CH_2Cl_2 (2×2 mL) and MeOH (2×2 mL). The resin was then treated with 2M NH_3 in MeOH (5 mL) and the mixture was shaken for 30 min. The solution was drained into a sample vial and the resin was resubmitted to NH_3/MeOH (2 mL) for another 30 min. The combined filtrate was concentrated to afford an oily residue, which was then transformed into a salt by treating with 2N HCl in ether.

EXAMPLE 5

The following Example describes the preparation of compound **60** from compound **47**. The synthetic steps in this Example are referenced to Scheme 5 set forth in **Figure 8**.

a. Production of compound 55 by debenzylation of compound 47

Compound **47** (5.42 g, 14.8 mmol) was dissolved in EtOAc (20 mL) and to the solution was added Pd/C (1.0 g) followed by AcOH (0.9 g, 14.8 mmol). The reaction mixture was saturated with H_2 by evacuating the air in the reaction vessel using an aspirator. The mixture was stirred at room temperature for 36h. The reaction was then filtered through a celite pad and rinsed with MeOH. The combined filtrate was purified by silica gel column chromatography using 45:5:1 CH_2Cl_2/MeOH/NH_4OH to afford 3.5 g of **55** as an off-white foam (85%); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 1.88 (d, J=12.8 Hz, 2H), 1.98 (quintet, J=7.2 Hz, 2H), 2.20 (dd, J=11.2 Hz, 2H), 2.92 (t, J=10.8 Hz, 2H), 3.26 (t, J=6.8 Hz, 2H), 3.53 (t, J=6.4 HZ, 2H), 3.56 (d, J=12.8 Hz, 2H), 4.19 (bs, 1H).

b. Production of compound 56 by acylation of compound 55

To a solution of compound **55** (0.30 g, 1.08 mmol) and Et_3N (0.16 g, 1.62 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of allyl chloroformate (0.16 g, 1.30 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. and washed with 1N HCl (10 mL) and saturated $NaHCO_3$ (10 mL). The organic layer was dried over Na_2SO_4 and concentrated. Silica gel column chromatography using 97:3 CH_2Cl_2/MeOH yielded 0.33 g of **56** as an off-white form (85%); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.55-1.69 (m, 4H), 1.96 (quintet, J=7.2 HZ, 2H), 2.78 (bs, 2H), 3.19 (bs, 2H), 3.52 (t, J=6.4 Hz, 2H), 4.25 (bs, 2H), 4.57 (d, J=5.6 HZ, 2H), 5.20 (dd, J=1.2 Hz, J=10.4 Hz, 1H), 5.28 (dd, J=1.6 HZ, J=17.2 Hz, 1H), 5.92 (ddd, J=5.6 Hz, J=10.4 Hz, J=17.2 Hz, 1H).

c. Conversion of chloro (56) to azido (57)

The azide derivative **57** was prepared in quantitative yield according to the procedure described previously (*see*, Example 1, part *c*); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.52-1.67 (m, 4H), 1.76 (quintet, J=6.8 Hz, 2H), 2.77 (bs, 2H), 3.11 (bs, 2H), 3.29 (t, J=6.4 Hz, 2H), 4.24 (bs, 2H), 4.57 (d, J=5.2 Hz, 2H), 5.20 (dd, J=1.2 Hz, J=12.0 HZ, 1H), 5.28 (dd, J=1.6 Hz, J=17.2 Hz, 1H), 5.93 (ddd, J=1.2 Hz, J=12.0 Hz, J=17.2 Hz, 1H).

d. Reduction of azide (57) to amine (58)

Azide **57** was converted to amine **58** according to the procedure described previously, (*see*, Example 1, part *d*).

e. Synthesis of amide (59) by acylation of amine (58)

Amide **59** was prepared in 90% yield according to the procedure described previously, (*see*, Example 1, part *e*); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 1.72 (bs, 6H), 2.81 (bs, 2H), 3.31-3.43 (m, 4H), 3.71 (bs, 1H), 3.89 (s, 6H), 4.28 (bs, 2H), 4.59 (d, J=5.2 Hz, 2H), 5.06 (s, 2H), 5.22 (d, J=10.4 Hz, 1H), 5.31 (d, J-17.6 Hz, 1H), 5.94 (ddd, J=10.4 Hz, J=17.6 Hz, 1H), 7.21 (s, 2H), 7.29-7.36 (m, 3H), 7.48 (d, J=7.2 Hz, 2H), 8.10 (bs, 1H).

f. Synthesis of amine (60) by deprotection of piperidine amide (59)

In an oven-dried round-bottomed flask, TBAF·xH_2O (1.04 g, 3.96 mmol) was dissolved in dry CH_2Cl_2 (10 mL). To the solution was added $TMSN_3$ (1.22 g, 10.6 mmol) followed by $Pd(PPh_3)_4$ (0.30 g, 0.26 mmol). Compound **59** (0.81 g, 1.32 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the reaction mixture at room temperature. The mixture was stirred for 30 min. under N_2 atmosphere and the solvent was removed to afford an orange oily residue. Silica gel column chromatography using 45:5:1 CH_2Cl_2/MeOH/NH_4OH afforded 0.53 g of amine **60** as a colorless oil (76%); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 1.62-1.80 (m, 6H), 2.63 (t, J=9.6 Hz, 2H), 3.15 (d, J=12.4 Hz, 2H), 3.44 (t, J=6.0 Hz, 2H), 3.41-3.48 (m, 2H), 3.71 (bs, 1H), 3.89 (s, 6H), 5.06 (s, 2H), 7.22 (s, 2H), 7.29-7.36 (m, 3H), 7.48 (d, J=6.8 Hz, 2H), 8.20 (bs, 1H).

EXAMPLE 6

This Example describes the general procedures used to assemble libraries of the compounds of the invention based on the scaffold of compound **60**. The library assembly steps described herein are referenced to Scheme 6 set forth in **Figure 9**.

In a parallel format, a solution of the amine **60** (50 mg, 0.095 mmol) in MeOH (1 mL) was placed in a sample vial. To the solution was added the aldehyde (0.47 mmol) in MeOH (1 mL) followed by $NaCNBH_3$ (30 mg, 0.47 mmol). The pH of the reaction mixture was adjusted to ~ 6 by adding AcOH (50 μL). The reaction mixture was stirred at room temperature for 48h and then diluted with CH_2Cl_2 (3 mL). An ion exchange resin (1 mL resin bed) was added to the solution and stirred for 20h. The resin was filtered using a cartridge and rinsed with MeOH (2×3 mL). The resin was then eluted with 2 M NH_3 in MeOH (2×3 mL) and the filtrate was concentrated. A short plug of silica gel column chromatography of the product using 45:5:1 CH_2Cl_2/MeOH/NH_4OH yielded a pure compound **22-33** (34-94% yield). Each compound was stored as a HCl salt

which was obtained by treating an oily residue with 1M HCl/ether after evaporating the solvent.

EXAMPLE 7

The following Example describes the preparation of compounds **37-40** using a multistep procedure. The synthetic steps in this Example are referenced to Scheme 7 set forth in **Figure 10**.

a. Synthesis of amides (61) and (62) by amidation of a benzoic acid precursor

4-Benzoyloxybenzoic acid (1.0 g, 4.38 mmol) was dissolved in CH_2Cl_2 (150 mL) and N-hydroxysuccinimide (0.61 g, 5.26 mmol) and DCC (1.09 g, 5.26 mmol) were added. The reaction mixture was stirred at room temperature for 1h and the white precipitate was filtered off. The filtrate was then added dropwise over 4h to a solution of 1,3-diaminopropane (3.25 g, 43.8 mmol) in CH_2Cl_2 (100 mL). The reaction solution was washed with water (5×250 mL) and the organic phase was dried over Na_2SO_4, then concentrated to yield 1.03 g of **61** as a colorless oil (82%); ^{1}H NMR ($CDCl_3$) δ 1.71 (quintet, J=6.0 Hz, 2H), 2.88 (t, J=6.0 HZ, 2H), 3.5 (q, J=6.0 Hz, 2H), 5.09 (s, 2H), 6.98 (d, J=8.8 Hz, 2H), 7.31-7.44 (m, 5H), 7.76 (d, J=8.8 Hz, 2H).

Compound **62** was prepared following the same procedure as above in 90% yield; ^{1}H NMR ($CDCl_3$) δ 1.65 (bs, 2H), 1.73 (quintet, J=6.4 H, 2H), 2.91 (t, J= 6.0 Hz, 2H), 3.55 (q, J= 5.6 Hz, 2H), 3.83 (s, 6H), 5.03 (s, 2H), 7.02 (s, 2H), 7.27-7.34 (m, 3H), 7.45 (d, J=6.4 Hz, 2H), 7.75 (bs, 1H).

b. Reductive amination with amines (61) and (62)

A mixture of amine (1 eq.) and ketone (1 eq.) in DCE (0.2 M) was treated with $NaBH(OAc)_3$ (1.5 eq.). The pH of the reaction mixture was adjusted to ~ 6 by adding AcOH. The mixture was stirred at room temperature for 12h and then treated with saturated $NaBHCO_3$. The aqueous phase was separated from the organic phase and re-extracted with CH_2Cl_2 (2×). The combined organic phase was dried over Na_2SO_4 and concentrated. Silica gel column chromatography using 45:5:1 CH_2Cl_2/MeOH/NH_4OH afforded a pure product (**37**: 81%, **38**: 78%).

c. Reduction of the amide

The corresponding amine was prepared according to the procedure described previously (**39**: 79%, **40**: 44%), (*see*, Example **1**, part *g*).

EXAMPLE 8

The following Example describes the preparation of compounds **12-13** and **41-42** from a common precursor compound. The synthetic steps in this Example are referenced to Scheme 8 set forth in **Figure 11**.

a. Acylation of the phenylamine

To 4-benzyloxyaniline HCl (1.83 g, 7.74 mmol) in DMF (3 mL) was added a pre-mixed solution of N-Boc-4-aminobutyric acid (1.31 g, 6.45 mmol), TBTU (2.48 g, 7.74 mmol) and DIPEA (2.08 g, 16.1 mmol) in DMF (7 mL). The reaction mixture was stirred at room temperature for 18h under N_2. The mixture was concentrated *in vacuo* and the residue was diluted with CH_2Cl_2 (20 mL). The solution was washed with aq. 1N HCl (15 mL), saturated $NaHCO_3$ (15 mL) and then water (10 mL). The organic phase was dried over Na_2SO_4 and concentrated. Silica gel column chromatography of the crude product using 49:1 CH_2Cl_2/MeOH afforded 2.2 g of **64** as a light brownish solid (90%); ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.88 (quintet, J=6.4 Hz, 2H), 2.37 (t, J=6.8 Hz, 2H), 3.26 (q, J=5.6 HZ, 2H), 4.81 (bs, 1H), 5.05 (s, 2H), 6.94 (d, J=9.2 Hz, 2H), 7.32 (t, J=6.8 Hz, 1H), 7.39 (t, J=7.2 Hz, 2H), 7.42 (t, J=7.2 Hz, 2H), 7.52 (d, J=8.8 Hz, 2H), 8.61 (bs, 1H). The compound **63** with β-alanine linker was prepared in 93% yield using the same procedure; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.64 (bs, 1H), 2.59 (t, J=6.0 Hz, 2H), 3.49 (q, J= 6.0 Hz, 2H), 5.03 (s, 2H), 5.18 (bs, 1H), 6.94 (d, J=9.2 Hz, 2H), 7.33-7.44 (m, 7H), 7.59 (bs, 1H).

b. Deprotection of the amine

The Boc-group was removed according to the procedure described previously (*see*, Example 2, part *d*).

c. Reductive amination

Each compound was prepared according to the procedure described previously (**12**: 85%, **13**:77%, **41**: 80%, **42**: 77%), (*see*, Example 7, part *b*).

EXAMPLE 9

The following Example describes the preparation of compounds **43** and **44** from compound **55**. The synthetic steps in this Example are referenced to Scheme 9 set forth in **Figure 12**.

a. Acylation of piperidine amine group

Amide **65** was prepared according to the procedure described previously (R_a: 95%, R_b: 90%), (*see*, Example 3, part *c*).

b. Conversion of chloro (65) to azide (66)

Compound **66** was prepared according to the procedure described previously (R_a: 94%, R_b: 87%), (*see*, Example 1, part *c*).

c. Reduction of azide (66) to amine (67)

Compound **67** was prepared according to the procedure described previously (R_a: 88%, R_b: 90%), (*see*, Example 1, part *d*).

d. Reductive amination with amine (67)

Compound **68** was prepared according to the procedure described previously (R_a: 61%, R_b: 70%), (*see*, Example 7, part *b*).

e. Deprotection of amine

The compounds **43** and **4 4** were prepared according to the procedure described previously (R_a: 94%, R_b: 91%), (*see*, Example 2, part *d*).

EXAMPLE 10

The following Example describes the preparation of compound **45** from compound **69**. The synthetic steps in this Example are referenced to Scheme 5 set forth in **Figure 13**.

a. Benzylation of piperidine amine group

To a solution of the amine **69** (50 mg, 0.092 mmol) in MeOH (2 mL) was added benzaldehyde (0.05 g, 0.46 mmol) followed by $NaCHBH_3$ (0.03 g, 0.46 mmol). AcOH was added to the reaction mixture until when the pH of the solution reached ~6. The mixture was stirred at room temperature for 12 h under N_2. The mixture was then diluted with $CHCl_3$ (3 mL) and an ion exchange resin (1 mL resin bed) was added, then shaken for 6h. The resin was filtered using a cartridge and washed with MeOH (3×5 mL). The resin was then eluted with 2 M NH_3/MeOH (2×5 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography using 45:5:1 CH_2Cl_2/MeOH/NH_4OH to afford **45** (50%).

EXAMPLE 11

This Example provides a tabulation of elemental analysis and NMR and mass spectral data for many of the compounds of the invention

Compound **1**: ^{1}H NMR (CD_3OD): δ 1.82-1.93 (m, 2H), 1.94-2.05 (m, 2H), 2.39 (d, J=13.6 Hz, 2H), 3.10-3.20 (m, 4H), 3.47 (t, J=6.4 Hz, 2H), 3.48-3.52 (m, 1H), 3.65 (d, J=13.2 Hz, 2H), 3.80 (s, 6H), 5.04 (s, 2H), 7.04 (s, 2H), 7.34-7.40 (m, 5H), 7.45-7.58 (m, 5H); MALDI calcd for $C_{31}H_{39}N_3O_4$=517.66, obsd=516.44.

Compound **2**: ^{1}H NMR ($CDCl_3$): δ 1.61 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.70 (d, J=10.3 Hz, 2H), 1.79 (quintet, J=5.6 Hz, 2H), 1.92 (dt, J=2.0 Hz, J=11.6 Hz, 2H), 2.35 (s, 3H), 2.47 (tt, J=4.0 Hz, J=11.6 Hz, 1H), 2.71 (t, J=5.6 Hz, 2H), 2.92 (d, J=12.0 Hz, 2H), 3.46 (s, 2H), 3.54 (dd, J= 5.2 Hz, J=11.2 Hz, 2H), 3.84 (s, 6H), 5.04 (s, 2H), 7.02 (s, 2H), 7.22-7.34 (m, 8H), 7.46 (d, J=8.4 Hz, 2H), 8.52 (t, J=4.9 Hz, 1H); MALDI calcd for $C_{32}H_{41}N_3O_4$=531.69, obsd=530.76; Anal Calcd for $C_{32}H_{41}N_3O_4$·2HCl: C, 63.57; H, 7.17; N, 6.95. Found C, 63.33; H, 7.28; N, 6.72.

Compound **3**: ^{1}H NMR ($CDCl_3$): δ 1.68 (d, J=10.4 Hz, 2H), 1.76 (quintet, J=6.0 Hz, 2H), 1.86 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 2.04 (t, J=12.0 Hz, 2H), 2.15 (s, 3H), 3.00 (d, J= 12.0 Hz, 2H), 3.36-3.39 (m, 2H), 3.44 (t, J= 6.4 Hz, 2H), 3.52 (s, 2H), 3.50-3.54 (m, 1H), 3,89 (s, 6H), 5.05 (s, 2H), 7.25 (s, 2H), 7.27-7.35 (m, 8H), 7.45-7.48 (m, 2H), 8.17 (t, J=5.1 Hz, 1H); MALDI calcd for $C_{33}H_{41}N_3O_5$=559.70, obsd=559.86.

Compound 4: ^{1}H NMR ($CDCl_3$): δ 1.66 (ddd, J=3.6 Hz, J=11.2 Hz, J=20.0 Hz, 2H), 1.96 (d, J=13. 6 Hz, 2H), 2.01 (t, J=11. 6 Hz, 2H), 2.83 (tt, J=4.0 HZ, J=10.0 Hz, 1H), 2.90 (d, J=12.0 Hz, 2H), 3.10 (t, J=5.2 Hz, 2H), 3.49 (s, 2H), 3.66 (q, J=4 Hz, 2H), 3.83 (s, 6H), 5.05 (s, 2H), 7.11 (s, 2H), 7.24-7.36 (m, 8H), 7.47 (d, J=8.0 Hz, 2H), 8.07 (bs, 1H); MALDI calcd for $C_{30}H_{37}N_3O_4$=503.63, obsd=502.25.

Compound 5: ^{1}H NMR ($CDCl_3$): δ 1.61-1.72 (m, 6H), 1.95 (d, J=10.4 Hz, 2H), 1.96 (t, J=12.4 Hz, 2H), 2.79 (tt, J=4.0 Hz, J=10.1 Hz, 2H), 2.86 (t, J=7.6 Hz, 2H), 2.89 (d, J=12.4 Hz, 2H), 3.36 (q, J=6.- Hz, 2H), 3.47 (s, 2H), 3.81 (s, 6H), 5.04 (s, 2H), 7.07 (s, 2H), 7.23-7.35 (m 8H), 7.45 (d, J=8.4 Hz, 2H); MALDI calcd for $C_{32}H_{41}N_3O_4$=531.69, obsd=530.56.

Compound 6: ^{1}H NMR (CD_3OD): δ 2.08 (dd, J=13.0 Hz, 22.0 Hz, 2H), 2.46 (d, J=13.3 Hz, 2H), 3.17 (t, J=14.0 Hz, 2H), 3.48-3.52 (m, 3H), 3.64 (d, J=18.0 Hz, 2H), 3,88 (s, 6H), 4.25 (s, 2H), 4.37 (s, 2H), 4.98 (s, 2H), 6.93 (s, 2H), 7.25-7.38 (m, 3H), 7.42-7.48 (m, 2H), 7.50-7.61 (m, 5H); MALDI calcd for $C_{30}H_{39}N_3O_3$=489.65, obsd=486.55.

Compound 7: ^{1}H NMR ($CDCl_3$): δ 1.37 (ddd, J=3.6 Hz, J= 12.2 Hz, J= 24.1 Hz, 2H), 1.63 (bs, 1H), 1.70 (quintet, J=6.8 Hz, 2H), 1.84 (d, J=12.4 Hz, 2H), 2.00 (dt, J=2.0 Hz, J=11.6 Hz, 2H), 2.43 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.71 (t, J=6.8 Hz, 2H), 2.84 (d, J=12.9 Hz, 2H), 3.48 (s, 2H), 3.71 (s, 2H), 3.82 (s, 6H), 4.98 (s, 2H), 6.54 (s, 2H), 7.22-7.36 (m, 8H), 7.49 (d, J=4.9 Hz, 2H); MALDI calcd for $C_{31}H_{41}N_3O_3$=503.68, obsd=502.12; Anal Calcd for $C_{31}H_{41}N_3O_3 \cdot 3HCl$: C, 60.73; H, 7.23; N, 6.85. Found C, 60.90; H, 7.27; N, 6.91.

Compound 8: ^{1}H NMR ($CDCl_3$): δ 1.38 (ddd, J=3.6 Hz, 2H), 1.52-1.60 (m, 3H), 1.84 (d, J=12.4 Hz, 2H), 2.01 (t, J=11.6 Hz, 2H), 2.46 (tt, J=4.0 Hz, J=10.4 Hz. 2H), 2.63-2.70 (m, 4H), 2.85 (d, J=12.9 Hz, 2H), 3.50 (s, 2H), 3.73 (s, 2H), 3.83 (s, 6H), 5.94 (s, 2H), 6.56 (s, 2H), 7.23-7.36 (m, 8H), 7.50 (d, J=7.2 Hz, 2H); MALDI calcd for $C_{32}H_{43}N_3O_3$=517.70, obsd=516.47.

Compound **9**: ^{1}H NMR ($CDCl_3$): δ 1.82-1.92 (m, 2H), 1.93-2.05 (m, 2H), 2.06-2.15 (m, 2H), 2.18-2.28 (m, 2H), 2.88-3.92 (m, 3H), 3.94-3.13 (m, 2H), 3.44-3.52 (m, 2H), 3.83 (s, 6H), 4.41 (s, 2H), 4.99 (s, 2H), 6.55 (s, 2H), 7.21-7.40 (m, 8H), 7.49 (d, J=6.8 Hz, 2H); MALDI calcd for $C_{31}H_{40}N_2O_4$=504.66, obsd=503.19.

Compound **10**: ^{1}H NMR (CD_3OD): δ 1.54 (ddd, J=3.6 Hz, J=12.0 Hz, J=24.0 Hz, 2H), 1.80-1.98 (m, 4H), 2.07 (dt (J=12.0 Hz, 2H), 2.92-3.02 (m, 3H), 3.06 (t, J=7.2 Hz, 2H), 3.54 (s, 2H), 3.60 (t, J=5.6 Hz, 2H), 4.44 (s, 2H), 5.08 (s, 2H), 6.98 (d, J=8.8 Hz, 2H), 7.27 (d, 8.8 Hz, 2H), 7.28-7.37 (m, 8H), 7.38-7.43 (m, 2H); MALDI calcd for $C_{29}H_{36}N_2O_2$=441.61, obsd=444.05.

Compound **11**: ^{1}H NMR ($CDCl_3$): δ 1.39 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.82 (d, J=12.0 Hz, 2H), 2.00 (t, J=11.2 Hz, 2H), 2.44 (t, J=6.0 Hz, 2H), 2.45-2.53 (m, 1H), 2.80 (d, J=11.6 Hz, 2H), 2.93 (t, J=6.0 Hz, 2H), 3.51 (s, 2H), 4.35 (d, J=5.6 Hz, 2H), 5.04 (s, 2H), 6.93 (d, J=8.8 Hz, 2H), 7.20 (d, J=8.8 Hz, 2H), 7.25-7.44 (m, 10H), 8.14 (t, J=5.6 Hz, 1H); MALDI calcd for $C_{29}H_{35}N_3O_2$=517.66, obsd=456.56; Anal Calcd for $C_{29}H_{35}N_3O_2$·2HCl: C, 65.65; H, 7.03; N, 7.92. Found C, 65.64; H, 6.82; N, 7.82.

Compound **12**: ^{1}H NMR ($CDCl_3$): δ 1.50 (ddd, J=3.6 Hz, J=3.6 Hz, J=11.2 Hz, J=20.0 Hz, 2H), 1.95 (d, J=12.4 Hz, 2H), 2.06 (t, J=11.2 Hz, 2H0, 2.33 ((bs, 1H), 2.52 (t, J=6.0 Hz, 2H), 2.57 (tt, J=4.9 Hz, J=10.8 Hz, 1H), 2,90 (d, J=12.0 Hz, 2H), 3.00 (t, J=6.0 Hz, 2H), 3.53 (s, 2H), 5.04 (s, 2H), 6.92 (d, J=6.8 Hz, 2H), 7.22-7.47 (m, 12H); MALDI calcd for $C_{28}H_{33}N_3O_2$=443.58, obsd=441.97; Anal Calcd for $C_{28}H_{33}N_3O_2$·2HCl: C, 65.11; H, 6.83; N, 8.14. Found C, 65.97; H, 6.79; N, 8.07.

Compound **13**: ^{1}H NMR ($CDCl_3$): δ 1.41 (ddd, J=3.2 Hz, J=11.8 Hz, J=23.1 Hz, 2H), 1.75 (bs, 1H), 1.78-1.98 (m, 4H), 2.01 (dt, J=2.0 Hz, J=11.6 Hz, 2H), 2.46 (t, J=6.8 Hz, 2H), 2.45-2.51 (m, 1H), 2.75 (t, J=6.4 Hz, 2H), 2.86 (d, J=12.0 Hz, 2H), 3.51 (s, 2H), 5.04 (s, 2H), 6.92 (d, J=8.8 Hz, 2H), 7.24-7.45 (m, 10H), 7.44 (d, J=8.8 Hz, 2H), 8.90 (s, 1H); MALDI calcd for $C_{29}H_{35}N_3O_2$=457.61, obsd=455.91; Anal Calcd for $C_{29}H_{35}N_3O_2$·2HCl: C, 65.65; H, 7.03; N, 7.92. Found C, 65.54; H, 6.99; N, 7.79.

Compound **14**: ^{1}H NMR ($CDCl_3$): δ 1.40 (ddd, J=3.6 Hz, J=12.4 Hz, J=24.1 Hz, 2H), 1.52 (bs, 1H), 1.66 (d, J=12.0 Hz, 2H), 1.68 (quintet, J=6.4 Hz, 2H), 1.89 (dt, J=2.4 Hz, J=11.6 Hz, 2H), 2.28 (tt, J=4.0 Hz, 10.4 Hz, 1H), 2.65 (t, J=6.4 Hz, 2H), 2.73 (d, J=12.0 Jz, 2H), 3.44 (s, 2H), 3.48 (q, J=6.0 Hz, 2H), 4.70 (s, 2H), 6.80 (d, J=7.2 Hz, 1H), 7.26-7.38 (m, 5H), 7.49-7.52 (m, 4H), 7.81-7.84 (m, 1H), 8.23-8.26 (m, 1H); MALDI calcd for $C_{29}H_{35}N_3O$=441.61, obsd=440.26; Anal Calcd for $C_{29}H_{35}N_3O$·2HCl: C, 67.70; H, 7.25; N, 8.17. Found C, 67.55; H, 7.37; N, 8.12.

Compound **15**: ^{1}H NMR ($CDCl_3$): δ 1.24 (ddd, J=3.6 Hz, J=12.4 Hz, J=24.1 Hz, 2H), 1.52 (bs, 1H), 1.66 (d, J=12.0 Hz, 2H), 1.68 (quintet, J=6.4 Hz, 2H), 1.89 (dt, J=2.4 Hz, J=11.6 Hz, 2H), 2.28 (tt, J=4.0 Hz, J=10.4 Hz, 1H), 2.65 (t, J=6.4 Hz, 2H), 2.73 (d, J=12.0 Hz, 2H), 3.44 (s, 2H), 3.48 (q, J=6..0 Hz, 2H), 4.70 (s, 2H), 6.80 (d, J=7.2 Hz, 1H), 7.26-7.38 (m, 5H), 7.49-7.52 (m, 4H), 7.81-7.84 (m, 1H), 8.23-8.26 (m., 1H); MALDI calcd for $C_{27}H_{33}N_3O_2$=431.57, obsd=429.74; Anal Calcd for $C_{27}H_{33}N_3O_2$·2HCl: C, 64.28; H, 6.99; N, 8.33. Found C, 64.31; H, 6.78; N, 8.18.

Compound **16**: ^{1}H NMR ($CDCl_3$) δ 1.38 (ddd, J=3.6 Hz, J=11.6 Hz, J=22.4 Hz, 2H), 1.70 (quintet, J= 6.4 Hz, 2H), 1.83 (d, J=12.4 Hz, 2H), 1.99 (dt, J=2.0 Hz, J=11.6 Hz, 2H), 2.42 (tt, J=4.0 Hz, J=10.8 Hz, 1H), 2.71 (t, J=6.4 Hz, 2H), 2.84 (d, J=12.0 Hz, 2H), 3.45 (q, J=6.4 Hz, 2H), 3.54 (s, 2H), 4.49 (s, 2H), 6.93 (d, J=8.8 Hz, 2H), 7.02 (t, J=7.2 Hz, 1H), 7.23-7.27 (m, 1H), 7.29-7.36 (m, 6H), 7.60 (bs, 1H); MALDI calcd for $C_{23}H_{31}N_3O$=381.51, obsd=381.69.

Compound **17**: ^{1}H NMR ($CDCl_3$) δ 1.45 (ddd, J=3.6 Hz, J=11.6 Hz, J=22.4 Hz, 2H), 1.81 (quintet, J=5.6 Hz, 2H), 1.91 (d, J=12.0 Hz, 2H), 2.01 (t, J=11.6 Hz, 2H), 2.42 (bs, 1H), 2.53 (tt, J=4.0 Hz, J=10.8 Hz, 1H), 2.86 (d, J=11.6 Hz, 2H), 2.91 (t, J=5.6 Hz, 2H), 3.48 (s, 2H), 3.60 (q, J=5.2 Hz, 2H), 7.23-7.28 (m, 1H), 7.29-7.34 (m, 4H), 7.37 (dd, J=8.0 Hz, J=4.8 Hz, 1H), 8.16 (td, J=2.0 Hz, J=8.0 Hz, 1H), 8.70 (dd, J=1.6 Hz, J=4.8 Hz, 1H), 8.80 (bs, 1H), 9.01 (d, J=2.0 Hz, 1H); MALDI calcd for $C_{21}H_{28}N_4O$=352.47, obsd=350.84.

Compound **18**: ^{1}H NMR ($CDCl_3$) δ 1.51 (ddd, J=4,0 Hz, J=12.0 Hz, J=24.0 Hz, 2H), 1.87 (quintet, J=6.4 Hz, 2H), 1.93 (d, J=12.4 Hz, 2H), 2.04 (t, J=11.6 Hz, 2H), 2.61 (tt, J=10.0 Hz, J=4.0 Hz, 1H), 2.82 (t, J=6.4 Hz, 2H), 2.88 (td, 2H), 3.51 (s, 2H), 3.59 (q, J=6.0 Hz,

2H), 7.23-7.28 (m, 1H), 7.29-7.35 (m, 4H), 7.43 (ddd, J=1.6 Hz, J=4.8 Hz, J=7.6 Hz, 1H), 7.85 (dt, J=7.6 Hz, J=1.6 Hz, 1H), 8.19 (d, J=8.0 Hz, 1H), 8.55 (d, J=4.8 Hz, 1H), 8.58 (bs, 1H); MALDI calcd for $C_{21}H_{28}N_4O$=352.47, obsd=351.14.

Compound **19**: ^{1}H NMR ($CDCl_3$) δ 1.38 (ddd, J=4.0 Hz, J=12.0 Hz, J=23.0 Hz, 2H), 1.63 (bs, 1H), 1.77 (quintet, J=5.6 Hz, 2H), 1.88 (d, J=12.0 Hz, 2H), 2.01 (dt, J=2.0 Hz, J=9.6 Hz, 2H), 2.47 (tt, J=4.0 Hz, J=10. 8 Hz, 1H), 2.86 (d, J=12.0 Hz, 2H), 2.89 (t, J=5.6 Hz, 2H), 3.07 (s, 3H), 3.49 (s, 2H), 3.59 (q, J=6.0 Hz, 2H), 7.23-7.35 (m, 5H), 7.99 (s, 4H), 8.98 (bs, 1H); MALDI calcd for $C_{23}H_{31}N_3O_3S$=429.58, obsd=428.32.

Compound **20**: ^{1}H NMR ($CDCl_3$) δ 1.39 (ddd, J=4.0 Hz, J=12.0 Hz, J=23.0 Hz, 2H), 1.58 (bs, 1H), 1.75 (quintet, J=6.0 Hz, 2H), 1.88 (d, J=12.0 Hz, 2H), 2.01 (dt, J=2.4 HZ, J=12.0 HZ, 2H), 2.47 (tt, J=4.4 Hz, J=10.8 Hz, 1H), 2.84 (t, J=5.6 Hz, 2H), 2.84 (d, J=12.0 Hz, 2H), 3.48 (s, 2H), 3.57 (q, J=5.2 Hz, 2H), 7.22-7.28 (m, 1H), 7.29-7.34 (m, 4H), 7.39-7.48 (m, 3H), 7.81 (dd, J=1.6 Hz, J=8.4 Hz, 2H), 8.35 (bs, 1H); MALDI calcd for $C_{22}H_{29}N_3O$=351.49, obsd=350.10.

Compound **21**: ^{1}H NMR (CD_3OD) δ 2.06-2.12 (m, 4H), 2.41 (d, J=11.6 Hz, 2H), 3.07 (t, J=6.8 Hz, 2H), 3.19-3.28 (m, 4H), 3.54-3.58 (m, 1H), 3.59 (d, J=12.4 Hz, 2H), 4.36 (s, 2H), 7.43-7.49 (m, 3H), 7.52-7.58 (m,2H); MALDI calcd for $C_{15}H_{25}N_3$=247.38, obsd=246.67.

Compound **22**: ^{1}H NMR ($CDCl_3$): δ 1.41 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.79 (quintet, J=6.0 Hz, 2H), 1.81 (bs, 1H), 1.93 (d, J=12.0 Hz, 2H), 2.04 (t, J=12.0 Hz, 2H), 2.45 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.57 (dd, J=6.0 Hz, J=10.8 Hz, 2H), 2.79 (dd, J=6.0 Hz, J=10.8 Hz, 2H), 2.85 (t, J=6.0 Hz, 2H), 2.96 (d, J=11.6 Hz, 2H), 3.56 (q, J=5.6 Hz, 2H), 3.86 (s, 6H), 5.05 (s, 2H), 7.02 (s, 2H), 7.19 (d, J=5.6 Hz, 2H), 7.27-7.36 (m, 3H), 7.47 (d, J=6.8 Hz, 2H), 7.98 (bs, 1H); MALDI calcd for $C_{32}H_{41}N_3O_4$=531.69, obsd=530.07; Anal Calcd for $C_{32}H_{41}N_3O_4$·2HCl: C, 63.57; H, 7.17; N, 6.95. Found C, 63.47; H, 6.94; N, 6.69.

Compound **23**: ^{1}H NMR ($CDCl_3$): δ 1.41 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.75 (quintet, J=6.0 Hz, 2H), 1.87 (d, J=11.2 Hz, 2H), 2.04 (t, 11.6 Hz, 2H), 2.45 (tt,

J=4.0 Hz, J=10.0 Hz, 1H), 2.84 (t, J=5.6 Hz, 2H), 2.88 (d, J=11.6 Hz, 2H), 3.56 (q, J=6.4 Hz, 2H), 3.63 (s, 2H), 3.87 (s, 6H), 5.06 (s, 2H), 7.03 (s, 2H), 7.28-7.36 (m, 3H), 7.45-7.49 (m, 5H), 7.71 (s, 1H), 7.79-7.84 (m, 3H), 8.14 (bs, 1H); MALDI calcd for $C_{35}H_{41}N_3O_4$=567.72, obsd=565.43; Anal Calcd for $C_{35}H_{41}N_3O_4 \cdot 2HCl$: C, 65.62; H, 6.76; N, 6.56. Found C, 65.48; H, 6.60; N, 6.52.

Compound **24**: ^1H NMR ($CDCl_3$): δ 0,84 (dd, J=11.2 Hz, 2H), 1.18-1.28 (m, 3H), 1.35-1.50 (m, 3H), 1.64-1.78 (m, 5H), 1.80 (quintet, J=6.0 Hz, 2H), 1.90 (t, J=11.2 Hz, 4H), 2.05 (bs, 1H), 2.08 (d, J=7.2 Hz, 2H), 2.46-2.53 (m, 1H), 2.83 (d, J=12.0 Hz, 2H), 2.87 (t, J=5.6 Hz, 2H), 3.57 (dd, J=4.6 Hz, J=5.6 Hz, 2H), 3.87 (s, 6H), 5.06 (s, 2H), 7.03 (s, 2H), 7.29-7.36 (m, 3H), 7.47 (d, J=6.8 Hz, 2H), 8.07 (bs, 1H); MALDI calcd for $C_{31}H_{45}N_3O_4$=523.71, obsd=522.29; Anal Calcd for $C_{31}H_{45}N_3O_4 \cdot 2HCl$: C, 62.41; H, 7.94; N, 7.04. Found C, 62.14; H, 7.84; N, 6.83.

Compound **25**: ^1H NMR ($CDCl_3$): δ 1.40 (ddd, J=3.0 Hz, J=12.0 Hz, J=24.1 Hz, 2H), 1.71 (bs, 1H), 1.76 (t, J=5.6 Hz, 2H), 1.89 (d, J=10.4 Hz, 2H), 2.05 (t, 11.2 Hz, 2H), 2.46 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.86 (t, J=5.6 Hz, 2H), 2.89 (d, J=11.6 Hz, 2H), 3.51 (s, 2H), 3.57 (q, J=6.0 Hz, 2H), 3.88 (s, 6H), 5.06 (s, 2H), 7.03 (s, 2H), 7.27-7.38 (m, 6H), 7.44-7.48 (m, 4H), 7.54-7.61 (m, 4H), 8.12 (bs, 1H); MALDI calcd for $C_{37}H_{43}N_3O_4$=593.76, obsd=591.36; Anal Calcd for $C_{37}H_{43}N_3O_4 \cdot 2HCl$: C, 66.66; H, 6.80; N, 6.30. Found C, 66.80; H, 7.00; N, 6.42.

Compound **26**: ^1H NMR ($CDCl_3$): δ 1.29 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.64 (bs, 1H), 1.75 (quintet, J=6.0 Hz, 2H), 1.82 (d, J=12.8 Hz, 2H), 2.02 (t, J=10.0 Hz, 2H), 2.40 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.83 (t, J=5.2 Hz, 2H), 2.90 (d, J=12.0 Hz, 2H), 2.95 (d, J=5.2 Hz, 2H), 3.55 (q, J=5.6 Hz, 2H), 3.78 (s, 6H), 4.18 (t, J=7.6 Hz, 1H), 5.05 (s, 2H), 7.00 (s, 2H), 7.16-7.37 (m, 13H), 7.48 (d, J=6.8 Hz, 2H), 8.11 (bs, 1H); MALDI calcd for $C_{38}H_{45}N_3O_4$=607.78, obsd=605.57.

Compound **27**: ^1H NMR ($CDCl_3$): δ 1.37 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.75 (quintet, J=5.6 Hz, 2H), 1.86 (d, 12.4 Hz, 2H), 2.03 (t, J=11.6 Hz, 2H), 2.43 (tt, J=4.0 Hz, J=10. 0 Hz, 1H), 2.82 (t, J=5.6 Hz, 2H), 2.94 (d, J=11.6 Hz, 2H), 3.55 (q, J=5.6 Hz, 2H), 3.68 (s, 2H), 3.76 (s, 3H), 3.81 (s, 6H), 5.05 (s, 2H), 6.99 (s, 1H), 7.01 (s, 2H),

7.12 (dt, J=1.2 Hz, J=6.8 Hz, 1H), 7.23 (dt, J=1.2 Hz, J=6.8 Hz, 1H), 7.29-7.36 (m, 4H), 7.47 (d, J=8.4 Hz, 2H(, 7.68 (d, 7.6 Hz, 1H), 8.05 (bs, 1H); MALDI calcd for $C_{34}H_{42}N_4O_4$=570.72, obsd=567.60; Anal Calcd for $C_{34}H_{42}N_4O_4 \cdot 3HCl$: C, 60.05; H, 6.67; N, 8.24. Found C, 63.31; H, 6.79; N, 8.07.

Compound **28**: ^1H NMR ($CDCl_3$): δ 1.38 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.76 (quintet, J=6.0 Hz, 2H), 1.87 (d, J=12.4 Hz, 2H), 2.02 (t, J=12.0 Hz, 2H), 2.44 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.58 (t, J=6.0 Hz, 2H), 2.83 (t, J=6.4 Hz, 2H), 2.90 (d, J=12.0 Hz, 2H), 3.55 (t, J=6.0 Hz, 2H), 3.56 (t, J=6.0 Hz, 2H), 3.86 (s, 6H), 4.53 (s, 2H), 5.05 (s, 2H), 7.01 (s, 2H), 7.28-7.36 (m, 8H), 7.47 (d, J=6.8 Hz, 2H), 7.99 (bs, 1H); MALDI calcd for $C_{33}H_{43}N_3O_5$=561.71, obsd=560.19.

Compound **29**: ^1H NMR ($CDCl_3$): δ 1.37 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.77 (quintet, J=6.0 Hz, 2H), 1.87 (d, J=12.0 Hz, 2H), 1.95 (t, J=12.0 Hz, 2H), 2.46 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.81 (d, J=12.0 Hz, 2H), 2.85 (t, J=5.6 Hz, 2H), 3.37 (s, 2H), 3.56 (q, J=4.0 Hz, 2H), 3.87 (s, 6H), 5.06 (s, 2H), 5.93 (s, 2H), 6.70 (dd, J=1.2 Hz, J=8.0 Hz, 1H), 6.74 (d, J=7.6 Hz, 1H), 6.82 (d, J=1.2 Hz, 1H), 7.02 (s, 2H), 7.28-7.36 (m, 3H), 7.47 (d, J=7.2 Hz, 2H), 8.10 (bs, 1H); MALDI calcd for $C_{32}H_{39}N_3O_6$=561.67, obsd=560.20; Anal Calcd for $C_{32}H_{39}N_3O_6 \cdot 2HCl$: C, 60.57; H, 6.51; N, 6.62. Found C, 60.46; H, 6.73; N, 6.65.

Compound **30**: ^1H NMR ($CDCl_3$): δ 1.37 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.59 (bs, 1H), 1.76 (quintet, J=5.6 Hz, 2H), 1.86 (d, J=12.4 Hz, 2H), 2.01 (t, J=11.6 Hz, 2H), 2.34 (s, 3H), 2.46 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.83 (d, J=11.6 Hz, 2H), 2.85 (t, J=6.0 Hz, 2H), 3.41 (s, 2H), 3.57 (q, J=5.6 Hz, 2H), 3.86 (s, 6H), 5.05 (s, 2H), 7.92 (s, 2H), 7.12-7.19 (m, 3H), 7.21-7.24 (m, 1H), 7.29-7.36 (m, 3H), 7.47 (d, J=6.8 Hz, 2H), 8.98 (bs, 1H); MALDI calcd for $C_{32}H_{41}N_3O_4$=531.69, obsd=529.82; Anal Calcd for $C_{32}H_{41}N_3O_4 \cdot 2HCl$: C, 63.57; H, 7.17; N, 6.95. Found C, 63.39; H, 7.01; N, 6.85.

Compound **31**: ^1H NMR ($CDCl_3$): δ 1.38 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.76 (quintet, J=5.6 Hz, 2H), 1.87 (d, J=11.6 Hz, 2H), 1.98 (t, J=11.6 Hz, 2H), 2.35 (s, 3H), 2.46 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.84 (t, J=6.0 Hz, 2H), 2.85 (d, J=11.6 Hz, 2H), 3.43 (s, 2H), 3.55 (q, J=6.0 Hz, 2H), 3.86 (s, 6H), 5.06 (s, 2H), 7.03 (s, 2H), 7.08 (t, J=7.2

Hz, 2H), 7.11 (s, 1H), 7.20 (t, J=7.2 Hz, 1H), 7.27-7.39 (m, 3H), 7.47 (d, J=6.8 Hz, 2H), 8.12 (bs, 1H); MALDI calcd for $C_{32}H_{41}N_3O_4$=531.69, obsd=529.68.

Compound **32**: ^{1}H NMR ($CDCl_3$): δ 1.34 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.76 (quintet, J=6.0 Hz, 2H), 1.87 (d, 12.0 Hz, 2H), 1.97 (t, J=11.6 Hz, 2H), 2.00 (bs, 1H), 2.46 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.79 (d, J=11.6 Hz, 2H), 2.82 (t, J=6.0 Hz, 2H), 3.45 (s, 1H), 3.48 (s, 2H), 3.55 (q, J=5.6 Hz, 2H), 3.86 (s, 6H), 5.06 (s, 2H), 6.00 (dd, J=2.8 Hz, J=5.6 Hz, 1H), 6.11 (dd, J=2.8 Hz, J=5.6 Hz, 1H), 6.74 (dd, J=2.8 Hz, J=4.2 Hz, 1H), 7.02 (s, 2H), 7.29-7.36 (m, 3H), 7.47 (d, J=8.4 Hz, 2H), 7.93 (bs, 1H); MALDI calcd for $C_{29}H_{38}N_4O_4$=506.64, obsd=504.45.

Compound **33**: ^{1}H NMR ($CDCl_3$) δ 1.39 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.74 (quintet, J=6.0 Hz, 2H), 1.87 (d, J=12.0 Hz, 2H), 2.02 (t, J=10.0 Hz, 2H), 2.42 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.81 (t, J=6.0 Hz, 2H), 2.84 (d, J=12.0 HZ, 2H), 3.49 (s, 2H), 3.53 (q, J=5.2 Hz, 2H), 3.84 (s, 6H), 5.04 (s, 2H), 6.17 (d, J=2.8 Hz, 1H), 6.30 (dd, J=2.0 Hz, J=2.8 Hz, 1H), 7.00 (s, 2h), 7.27-7.37 (m, 4H), 7.46 (d, J=6.8 Hz, 2H), 8.00 (bs, 1H); MALDI calcd for $C_{29}H_{37}N_3O_5$=507.62, obsd=506.40.

Compound **34**: ^{1}H NMR ($CDCl_3$) δ 1.20 (ddd, J=3.6 Hz, J=12.0 Hz, J=23.2 Hz, 2H), 1.77 (quintet, J=6.4 Hz, 2H), 1.75 (bs, 1H), 1.90 (d, J=12.4 Hz, 2H), 2.53 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.58 (dt, J=2.0 Hz, J=12.4 Hz, 2H), 2.84 (t, J=5.6 Hz, 2H), 3.07 (td, J=2.0 Hz, J=12.4 Hz, 2H), 3.55 (q, J=5.6 Hz, 2H), 3.86 (s, 6H), 5.05 (s, 2H), 7.01 (s, 2H), 7.27-7.35 (m, 3H), 7.46 (d, J=8.0 Hz, 2H), 7.92 (bs, 1H); MALDI calcd for $C_{24}H_{33}N_3O_4$=427.54, obsd=427.08.

Compound **35**: ^{1}H NMR ($CDCl_3$) δ 1.35 (ddd, J=3.6 Hz, J=12.4 Hz, J=22.6 Hz, 2H), 1.73 (quintet, J=6.0 Hz, 2H), 1.86 (d, J=12.4 Hz, 2H), 1.93 (t, J=11.6 Hz, 2H), 2.22 (s, 3H), 2.41 (tt, J=4.0 Hz, J=10.4 Hz, 1H), 2.76 (d, J=12. 0 Hz, 2H), 2.80 (t, J=6.0 Hz, 2H), 3.52 (q, J=6.4 Hz, 2H), 3.83 (s, 6H), 5.03 (s, 2H), 7.00 (s, 2H), 7.25-7.36 (m, 3H), 7.45 (d, J=8.0 Hz, 2H), 7.97 (t, J=4.8 Hz, 1H); MALDI calcd for $C_{25}H_{35}N_3O_4$=441.56, obsd=441.85.

Compound **36**: ^{1}H NMR ($CDCl_3$): δ 1.20-1.30 (m, 3H), 1.36-1.55 (m, 4H), 1.62-1.75 (m, 3H), 1.76-1.82 (m, 2H), 1.94 (quintet, J=5.6 Hz, 2H), 2.03 (d, J=12.0 Hz, 1H), 2.10 (d, J=12.0 Hz, 1H), 2.46 (t, J=11.6 Hz, 1H), 2.61 (t, J=11.6 Hz, 1H), 2.92 (t, J=6.0 Hz, 2H), 3.05 (t, J=12.0 Hz, 2H), 3.54 (q, J=5.6 Hz, 2H), 3.92 (d, J=12.0 Hz, 1H), 4.62 (d, J=12.0 Hz, 1H), 5.09 (s, 2H), 6.98 (d, J=8.8 Hz, 2H), 7.31-7.44 (m, 5H), 7.79 (d, 8.8 Hz, 2H); MALDI calcd for $C_{29}H_{39}N_3O_3$=477.64, obsd=475.99; Anal Calcd for $C_{29}H_{39}N_3O_3 \cdot HCl \cdot 0.9H_2O$: C, 65.68; H, 7.94; N, 7.92. Found C, 65.64; H, 7.60; N, 7.76.

Compound **37**: ^{1}H NMR ($CDCl_3$): δ 0.85 (dd, J=12.0 Hz, J=24.1 Hz, 2H), 1.13-1.27 (m, 3H), 1.38 –1.48 (m, 3H0, 1.62-1.82 (m, 7H), 1.82-1.93 (m, 4H), 2.06 (bs, H), 2.08 (d, J=6.8 Hz, 2H), 2.48 (tt, J=4.0 Hz, J=10.8 Hz, 1H), 2.83 (q, J=5.6 Hz, 2H), 5.10 (s, 2H), 6.99 (d, J=8.8 Hz, 2H), 7.32-7.44 (m, 5H), 7.78 (d, 8.8 Hz, 2H), 8.12 (bs, 1H); MALDI calcd for $C_{29}H_{41}N_3O_2$=463.65, obsd=461.40; Anal Calcd for $C_{29}H_{41}N_3O_2 \cdot 2HCl$: C, 64.91; H, 8.08; N, 7.83. Found C, 65.04; H, 7.98; N, 7.66.

Compound **38**: ^{1}H NMR ($CDCl_3$): δ 1.37 (ddd, J=3.6 Hz, J=12.0 Hz, J=24.1 Hz, 2H), 1.79 (quintet, J=5.6 Hz, 2H), 1.89 (d, J=12.0 Hz, 2H), 2.06 (t, J=11.6 Hz, 2H), 2.49 (tt, J=4.0 Hz, J=10.8 Hz, 1H), 2.82 (t, J=6.0 Hz, 2H), 2.89 (d, J=11.6 Hz, 2H), 2.97 (d, J=7.2 Hz, 2H), 3.54 (q, J=6.0 Hz, 2H), 4.20 (t, J=7.6 Hz, 1H), 5.09 (s, 2H), 6.97 (d, J=8.8 Hz, 2H), 7.16-7.20 (m, 2H), 7.24-7.30 (m, 8H), 7.35-7.46 (m, 5H), 7.80 (d, J=8.8 Hz, 2H), 8.28 (t, J=4.8 Hz, 1H); MALDI calcd for $C_{36}H_{41}N_3O_2$=547.73, obsd=547.83; Anal Calcd for $C_{36}H_{41}N_3O_2 \cdot 2HCl$: C, 69.67; H, 6.98; N, 6.77. Found C, 69.88; H, 6.79; N, 6.54.

Compound **39**: ^{1}H NMR ($CDCl_3$): δ 0.85 (dd, 12.2 Hz, J=24.1 Hz, 2H), 1.13-1.26 (m, 3H), 1.36 (ddd, J=3.6 Hz, J=12.4 Hz, J=24.1 Hz, 2H), 1.42-1.50 (m, 1H), 1.64-1.80 (m, 9H), 1.81-1.92 (m, 4H), 2.08 (d, J=7.2 Hz, 2H), 2.41 (tt, J=3.2 Hz, J=8.4 Hz, 1H), 2.72 (dt, J=1.6 Hz, J=6.8 Hz, 2H), 2.81 (d, J=12.0 Hz, 2H), 3.72 (s, 2H), 3.83 (s, 6H), 4.99 (s, 2H), 6.5 (s, 2H), 7.28-7.49 (m, 3H), 7.50 (d, J=8.4 Hz, 2H); MALDI calcd for $C_{31}H_{47}N_3O_3$=509.72, obsd=507.88; Anal Calcd for $C_{31}H_{47}N_3O_3 \cdot 3HCl$: C, 60.14; H, 8.14; N, 6.79. Found C, 60.02; H, 7.94; N, 6.72.

Compound **40**: ^{1}H NMR ($CDCl_3$): δ 1.29 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.72 (quintet, J=6.8 Hz, 2H), 1.79 (d, J=11.6 Hz, 2H), 1.96 (bs, 1H), 2.05 (dt, J=2.0 Hz, J=9.6 Hz, 2H), 2.41 (tt, J=3.2 Hz, J=8.4 Hz, 1H), 2.71 (dt, J=2.0 Hz, J=6.8 Hz, 2H), 2.87

(d, J=11.6 Hz, 2H), 2.96 (d, J=7.6 Hz, 2H), 3.72 (s, 2H), 3.81 (s, 6H), 4.19 (t, J=8.0 Hz, 1H), 4.99 (s, 2H), 6.54 (s, H), 7.19-7.20 (m, 2H), 7.23-7.31 (m, 9H), 7.33-7.37 (m, 2H), 7.51 (d, J=8.0 Hz, 2H); MALDI calcd for $C_{38}H_{47}N_3O_3$=593.80, obsd=590.09; Anal Calcd for $C_{38}H_{47}N_3O_3 \cdot 3HCl$: C, 64.91; H, 7.17; N, 5.98. Found C, 64.72; H, 7.12; N, 5.80.

Compound **41**: ^1H NMR ($CDCl_3$): δ 1.38 (ddd, J=3.6 Hz, J=12.0 Hz, J=24.1 Hz 2H), 1.88 (d, J=11.2 Hz, 2H), 2.05 (bs, 1H), 2.10 (t, J=11.2 Hz, 2H), 2.50 (t, J=6.0 Hz, 2H), 2.53 (tt, J=4.0 Hz, J=10.0 Hz, 1H), 2.91 (d, J=12.0 Hz, 2H), 2.97 (t, J=5.6 Hz, 2H), 3.00 (d, J=7.2 Hz, 2H), 4.22 (t, J=7.6 Hz, 1H), 5.05 (s, 2H), 6.92 (d, J=9.2 Hz, 2H), 7.18-7.23 (m, 2H), 7.24-7.33 (m, 9H), 7.36-7.46 (m, 6H); MALDI calcd for $C_{35}H_{39}N_3O_2$=533.70, obsd=532.07; Anal Calcd for $C_{35}H_{39}N_3O_2 \cdot 2HCl$: C, 69.30; H, 6.81; N, 6.93. Found C, 69.15; H, 7.02; N, 6.88.

Compound **42**: ^1H NMR ($CDCl_3$): δ 0.87 (ddd, J=3.6 Hz, J=12. 0 Hz, J=24.1 Hz, 2H), 1.11-1.28 (m, 3H), 1.43-1.52 (m, 3H), 1.62-1.80 (m, 4H), 1.88-2.02 (m, 4H), 2.12 (d, J=6.8 Hz, 2H), 2.50 (t, J=5.6 Hz, 2H), 2.54 (tt, J=4.0 Hz, J=10.8 Hz, 1H), 2.86 (d, J=12.0 Hz, 2H), 3.00 (t, J=5.6 Hz, 2H), 5.04 (s, 2H), 6.92 (d, J=9.2 Hz, 7.30-7.47 (m, 7H); MALDI calcd for $C_{28}H_{39}N_3O_2$=449.63, obsd=447.19; Anal Calcd for $C_{28}H_{39}N_3O_2 \cdot 2HCl$: C, 64.36; H, 7.91; N, 8.04. Found C, 64.20; H, 7.74; N, 7.89.

Compound **43**: ^1H NMR ($CDCl_3$): δ 1.20-1.40 (m, 5H), 1.43-1.58 (m, 2H), 1.65-1.73 (m, 3H), 1.85-1.95 (m, 6H), 2.46 (tt, J=3.2 Hz, J=8.4 Hz, 1H), 2.64 (t, J=11.6 Hz, 1H), 2.74 (tt, J=3.6 Hz, J=10.8 Hz, 1H), 2.79-2.90 (m, 4H), 3.03 (t, J=12.8 Hz, 1H), 3.81 (d, J=4.0 Hz, 2H), 3.88 (d, J=14.4 Hz, 1H), 4.52 (d, J=13.2 Hz, 1H), 5.06 (s, 2H), 6.95 (d, J=8.8 Hz, 2H), 7.28 (d, J=8.8 Hz, 2H), 7.31-7.44 (m, 5H; MALDI calcd for $C_{29}H_{41}N_3O_2$=463.65, obsd=462.27; Anal Calcd for $C_{29}H_{41}N_3O_2 \cdot 2HCl$: C, 64.91; H, 8.08; N, 7.83. Found C, 64.84; H, 7.88; N, 7.74.

Compound **44**: ^1H NMR ($CDCl_3$): δ 1.05 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 2H), 1.24 (ddd, J=3.6 Hz, J=12.2 Hz, J=24.1 Hz, 1H), 1.75-1.88 (m, 4H), 2.66 (tt, J=3.2 Hz, J=8.4 Hz, 1H), 2.73-2.76 (m, 2H), 2.80 (q, J=6.0 Hz, 2H), 2.95-3.04 (m, 2H), 3.73 (s, 2H), 3.73 (d, J=2.4 Hz, 2H), 3.81 (d, J=13.2 Hz, 1H), 4.50 (d, J=13.2 Hz, 1H), 5.06 (s, 2H), 6.94 (d, J=8.8 Hz, 2H), 7.23-7.44 (m,12H); MALDI calcd for $C_{30}H_{37}N_3O_2$=471.63,

obsd=469.44; Anal Calcd for $C_{30}H_{37}N_3O_2 \cdot 2HCl$: C, 66.17; H, 7.22; N, 7.72. Found C, 66.16; H, 7.25; N, 7.72.

Compound **45**: ^1H NMR ($CDCl_3$): δ 1.25 (ddd, J=3.6Hz, J=12.4 Hz, J=24.2 Hz, 2H), 1.46 (tt, J=3.6 Hz, J=10.0 Hz, 1H), 1.67 (d, J=11.6 Hz, 2H), 1.80 (quintet, J=6Hz, 2H), 1.91 (dt, J=2.4 Hz, J=12.0 Hz, 2H), 2.22 (bs, 1H), 2.53 (d, J=6.8 Hz, 2H), 2.80 (t, J=5.6 Hz, 2H), 2.87 (d, J=11.6 Hz, 2H), 3.47 (s, 2H), 3.55 (q, J=5.6 Hz, 2H), 3.85 (s, 6H), 5.04 (s, 2H), 7.02 (s, 2H), 7.07-7.37 (m, 8H), 7.47 (d, J=8.0 Hz, 2H), 7.89 (bs, 1H); MALDI calcd for $C_{32}H_{41}N_3O_4$=531.69, obsd=530.29.

Compound **100**: ^1H NMR ($CDCl_3$) δ 0.99 (t, J=7.2 Hz, 6H), 1.27 (ddd, J=3.6 Hz, J=12.0 Hz, J=20.0 Hz, 2H), 1.60 (quintet, J=6.8 Hz, 2H), 1.76 (d, J=12.0 Hz, 2H), 2.05 (dt, J=2.0 Hz, J=11.6 Hz, 2H), 2.37 (tt, J=4.0 Hz, J=10.4 HZ, 1H), 2.43 (t, J=7.2 Hz, 2H), 2.48 (q, J=7.2 Hz, 4H), 2.61 (t, J=6.8 HZ, 2H), 2.85 (d, J=12.0 HZ, 2H), 2.94 (d, J=7.6 Hz, 2H), 4.17 (t, J=7.6 Hz, 1H), 7.13-7.17 (m, 2H), 7.21-7.29 (m, 8H); MALDI calcd for $C_{26}H_{39}N_3$=393.62: obsd=391.18.

Compound **110**: ^1H NMR ($CDCl_3$) δ 1.01 (t, J=7.2 Hz, 6H), 1.56 (ddd, J=2.8 Hz, J=11.8 Hz, J=22.0 Hz, 2H), 1.82 (quintet, J=6.4 Hz, 2H), 1.93 (d, J=10.4 Hz, 2H), 1.97 (t, J=12.0 Hz, 2H), 2.55 (q, J=6.8 Hz, 4H), 2.55 (t, J=7.6 Hz, 2H), 2.63 (tt, J=4.0 Hz, J=10.8 Hz, 1H), 2.84 (d, J=10.0 Hz, 2H), 2.85 (t, J=6.4 Hz, 2H), 3.44 (s, 2H), 6.40 (bs, 1H), 7.17-7.21 (m, 1H), 7.24-7.30 (m, 4H); MALDI calcd for $C_{19}H_{33}N_3$=303.49: obsd=301.55.

Compound **120**: ^1H NMR ($CDCl_3$) δ 1.27 (ddd, J=3.6 Hz, J=12.0 Hz, J=22.0 Hz, 2H), 1.67 (quintet, J=6.8 Hz, 2H), 1.76 (d, J=12.8 Hz, 2H), 1.75-1.82 (bs, 2H), 2.04 (dt, J-11.6 Hz, 2H), 2.38 (tt, J=4.0 Hz, J=10.4 Hz, 1H), 2.66 (dd, J=5.6 Hz, J=6.8 Hz, 4H), 2.85 (d, J=11.6 Hz, 2H), 2.94 (d, J=7.6 Hz, 2H), 3.70 (s, 2H), 4.18 (t, J=7.6 Hz, 2H), 5.04 (s, 2H), 6.92 (d, J=8.8 Hz, 2H), 7.16-7.28 (m, 13H), 7.38 (t, J=6.8 Hz, 2H), 7.42 (t, J=7.2 Hz, 2H); MALDI calcd for $C_{36}H_{43}N_3O$=531.87: obsd=533.76.

Compound **130**: MALDI calcd for $C_{38}H_{47}N_3O$=561.81: obsd=560.62.

Compound **140**: MALDI calcd for $C_{30}H_{37}N_3O_4$=503.60: obsd=502.72

Compound **150**: MALDI calcd for $C_{30}H_{39}N_3O_3$=489.66: obsd=488.85.

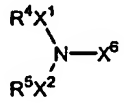
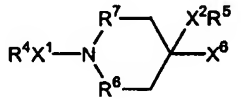
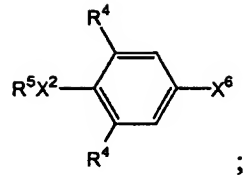
WHAT IS CLAIMED IS:

1. A compound having the structure:

$$R^1—R^2—R^3$$

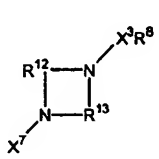
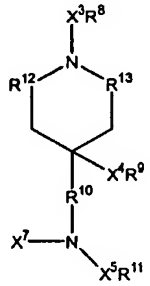
wherein,

R^1 is a member selected from



and

;

R^2 is a member selected from aryl, substituted aryl, heteroaryl, substituted heteroaryl, C_1-C_{10} alkyl and substituted C_1-C_{10} alkyl;

R^3 is a member selected from


and


wherein,

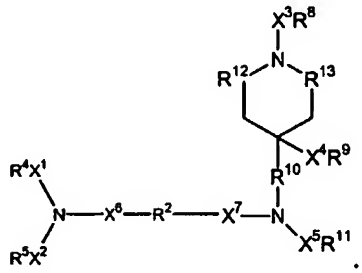
X^1, X^2, X^3, X^4, X^5, X^6, and X^7 are members independently selected from a single bond, —O—, —C(O)—, —CO_2—, —C(O)NH—, —C(O)NR^{14}—, and —SO_2—;

R^4, R^5, R^8, R^9 and R^{11} are members independently selected from H, —OH, alkoxy, C_1-C_{10} alkyl and C_1-C_{10} substituted alkyl;

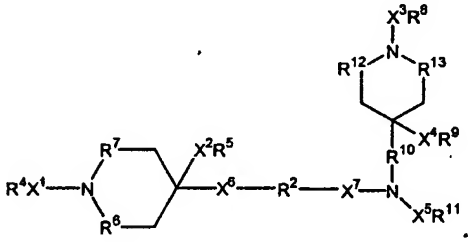
R^6, R^7, R^{10}, R^{12} and R^{13} are members independently selected from —C(O)—, —CO_2—, —C(O)NH—, —C(O)NR^{15}—, and —SO_2—; C_1-C_3 alkyl; and substituted C_1-C_3 alkyl; and

R^{14}, R^{15}, R^{16} and R^{17} are members independently selected from alkyl, aryl, heteroaryl, carboxy ester, carboxamide, amino, N-acylamino, alkoxy, hydroxy, mercapto, phosphono and sulfono groups.

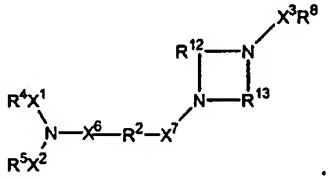
2. The compound according to claim 1, having the structure:



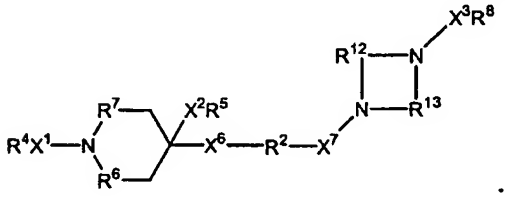
3. The compound according to claim 1, having the structure:



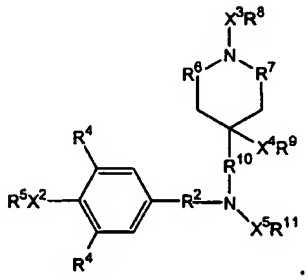
4. The compound according to claim 1, having the structure:



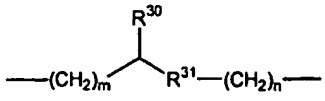
5. The compound according to claim 1, having the structure:



6. The compound according to claim 1, having the structure:



7. The compound according to claim 1, wherein R^2 has the structure:



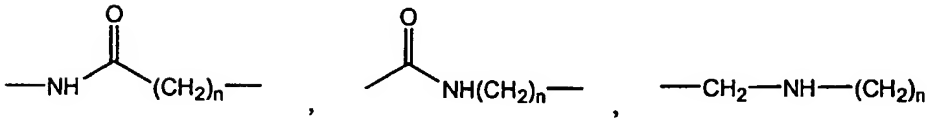
wherein,

R^{30} is a member selected from H and (=O);

R^{31} is selected from —NH— and —O—; and

m and n are numbers independently selected from 0 to 10, inclusive.

8. The compound according to claim 7, wherein R^2 has a structure selected from

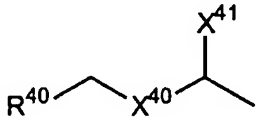


wherein,

n is an integer between 1 and 5, inclusive.

9. The compound according to claim 8, wherein n is an integer between 2 and 4, inclusive.

10. The compound according to claim 1, wherein R^1 has the structure:



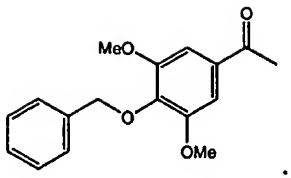
wherein,

R^{40} is a member selected from benzene, substituted benzene, and polycyclic hydrocarbons;

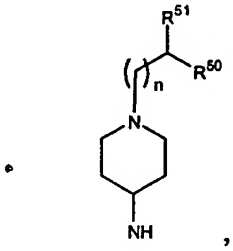
X^{40} is a member selected from —CH_2— and —O—;

X^{41} is a member selected from H and (C=O).

11. The compound according to claim 10, wherein R^1 has the structure:



12. The compound according to claim **1**, wherein R^3 has the structure:



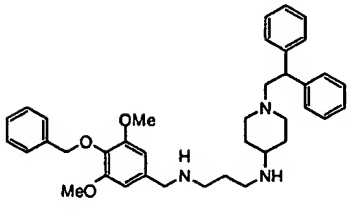
wherein

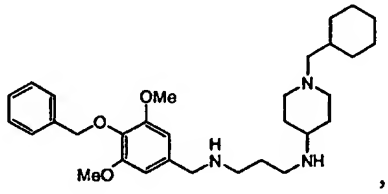
R^{50} and R^{51} are members independently selected from H, aryl, substituted aryl, heteroaryl and substituted heteroaryl groups; and

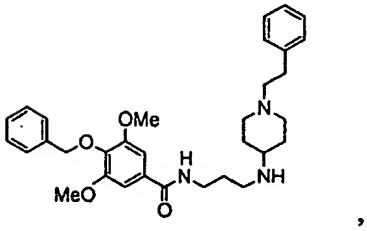
n is a number from 0 to 5.

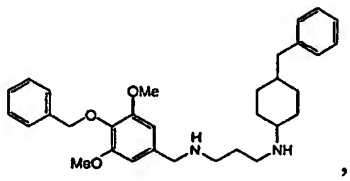
13. The compound according to claim **12**, wherein R^{50} and R^{51} are both benzene.

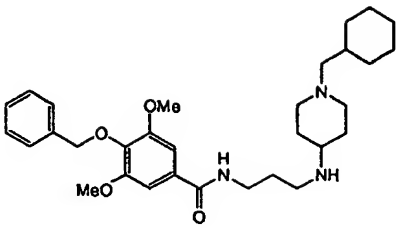
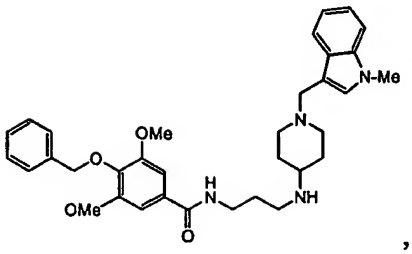
14. The compound according to claim **1**, having a structure selected from:

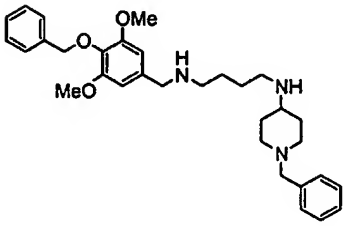
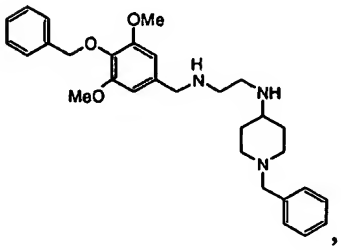


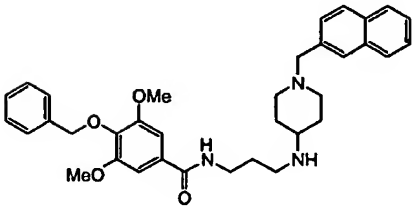
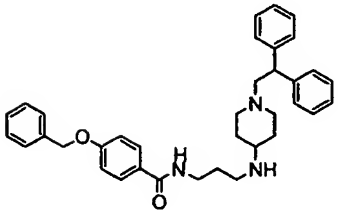


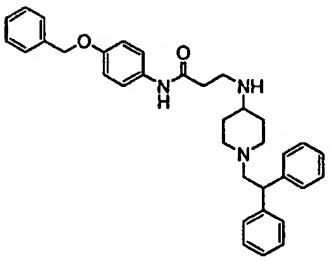
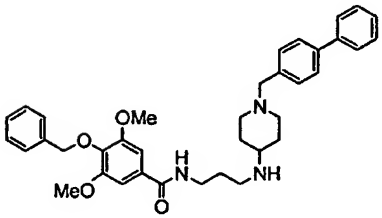


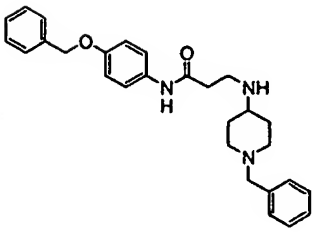
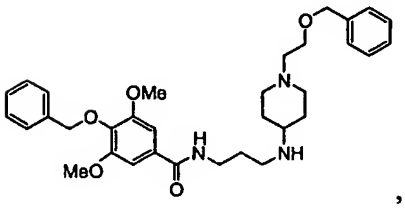


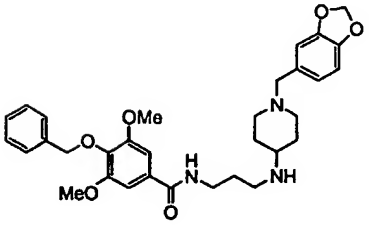
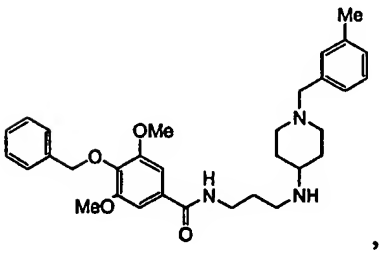
5  ,  ,

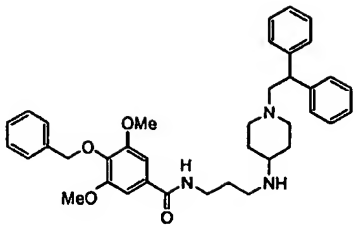
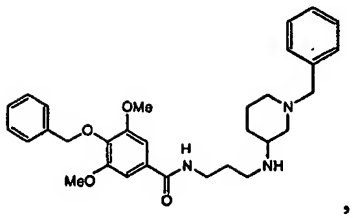
6  ,  ,

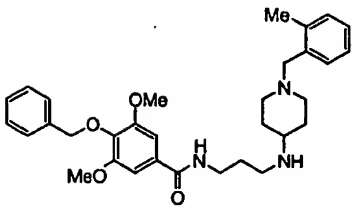
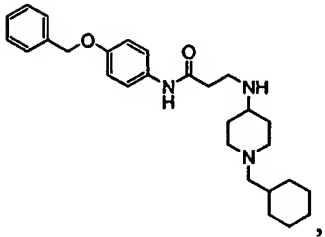
7  ,  ,

8  ,  ,

9  ,  ,

10  ,  ,

11  ,  ,

12  ,  ,

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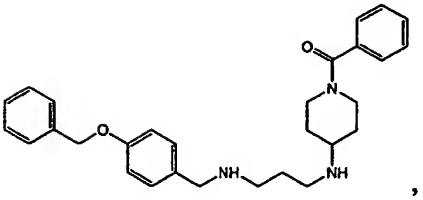
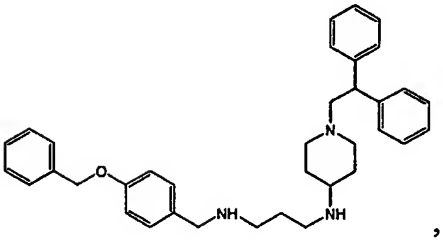
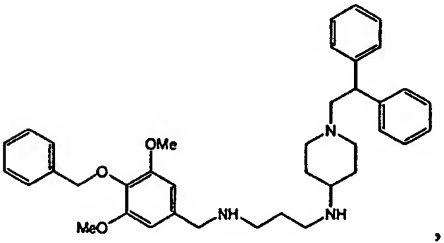
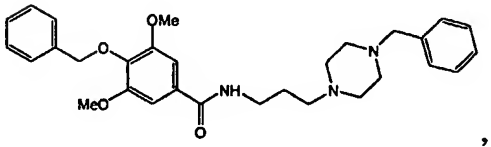
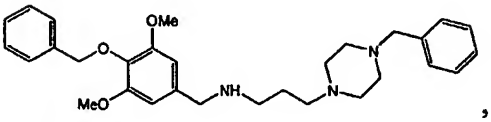
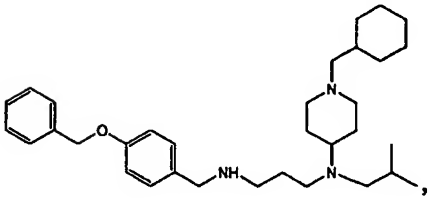
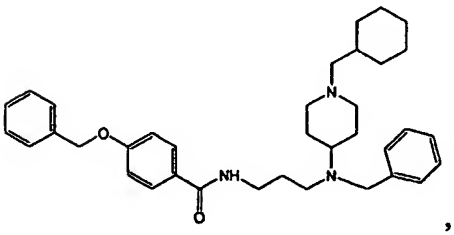
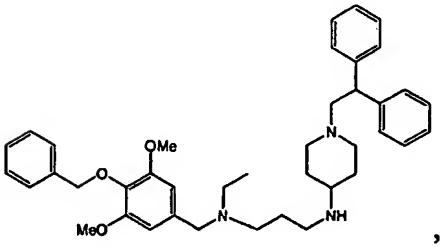
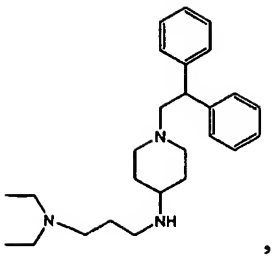
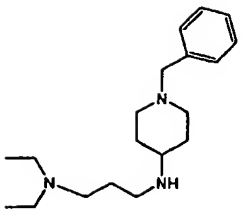
14  ,  ,

15  ,  ,

16  ,  ,

17  ,  ,

18  ,  .

15. The compound according to claim 1 having an IC50 towards a protozoal enzyme of less than 5000 nanomolar.

16. The compound according to claim 15 having an IC50 towards a protozoal enzyme of less than 1000 nanomolar.

17. The compound according to claim 16 having an IC50 towards a protozoal enzyme of less than 500 nanomolar.

18. The compound according to claim 17 having an IC50 towards a protozoal enzyme of less than 50 nanomolar.

19. The compound according to claim 18 having an IC50 towards a protozoal enzyme of from about 0.05 nanomolar to about 40 nanomolar.

20. The compound according to claim 19 having an IC50 towards a protozoal enzyme of from about 1 nanomolar to about 20 nanomolar.

21. The compound according to claim 1 that inhibits an enzyme selected from cysteine protease, aspartyl protease and combinations thereof.

22. The compound according to claim 21, wherein said enzyme comprises a component of an organism selected from Kinetoplastida, Apicomplexa, Anaerobic protozoa, Microsporidia and Plasmodium.

23. The compound according to claim 22, wherein said Plasmodium is *Plasmodium falciparum*.

24. The compound according to claim 1 that prevents or reduces heme polymerization mediated by *Plasmodium falciparum*.

25. A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

26. The pharmaceutical composition according to claim 25, further comprising at least one additional antiprotozoal agent.

27. The pharmaceutical composition according to claim 26, wherein said at least one additional antiprotozoal agent is active against a member selected from Kinetoplastida, Apicomplexa, Anaerobic protozoan, Microsporidia and Plasmodium.

28. The pharmaceutical composition according to claim 27, wherein said at least one additional antiprotozoal agent is active against a Plasmodium that causes malaria.

29. The pharmaceutical composition according to claim 28, wherein said at least one additional antiprotozoal agent is selected from artemether, arteether, artemisinine, dihydroartemisinine, artesunate, quinidine, mefloquine and combinations thereof.

30. An unit dose formulation comprising a compound according to claim 1 in an amount from about 10 mg to about 3 g.

31. An unit dose formulation comprising a compound according to claim 1 in an amount from about 50 mg to about 1 g.

32. A method of treating or preventing a protozoal infection in a subject, said method comprising:

(a) administering to said subject the pharmaceutical composition of claim 25, in an amount effective to treat or prevent said infection.

33. The method according to claim 32, wherein said protozoan is a member selected from Kinetoplastida, Apicomplexa, Anaerobic protozoan, Microsporidia and Plasmodium.

34. The method according to claim 33, wherein said protozoan is a causative agent of malaria.

35. A method for interrupting the reproductive cycle of a protozoan, said method comprising:

(a) contacting said protozoan with a compound according to claim **1**, in an amount effective to interrupt said reproductive cycle.

36. A method for inhibiting a protozoal enzyme, said method comprising:

(a) contacting said enzyme with a compound according to claim **1**, in an amount effective to inhibit said enzyme.

37. The method according to claim **36**, wherein said enzyme is a digestive enzyme of said protozoan.

38. The method according to claim **36**, wherein said enzyme is a protease is a member selected from serine, cysteine, aspartyl, metalloproteases and combinations thereof.

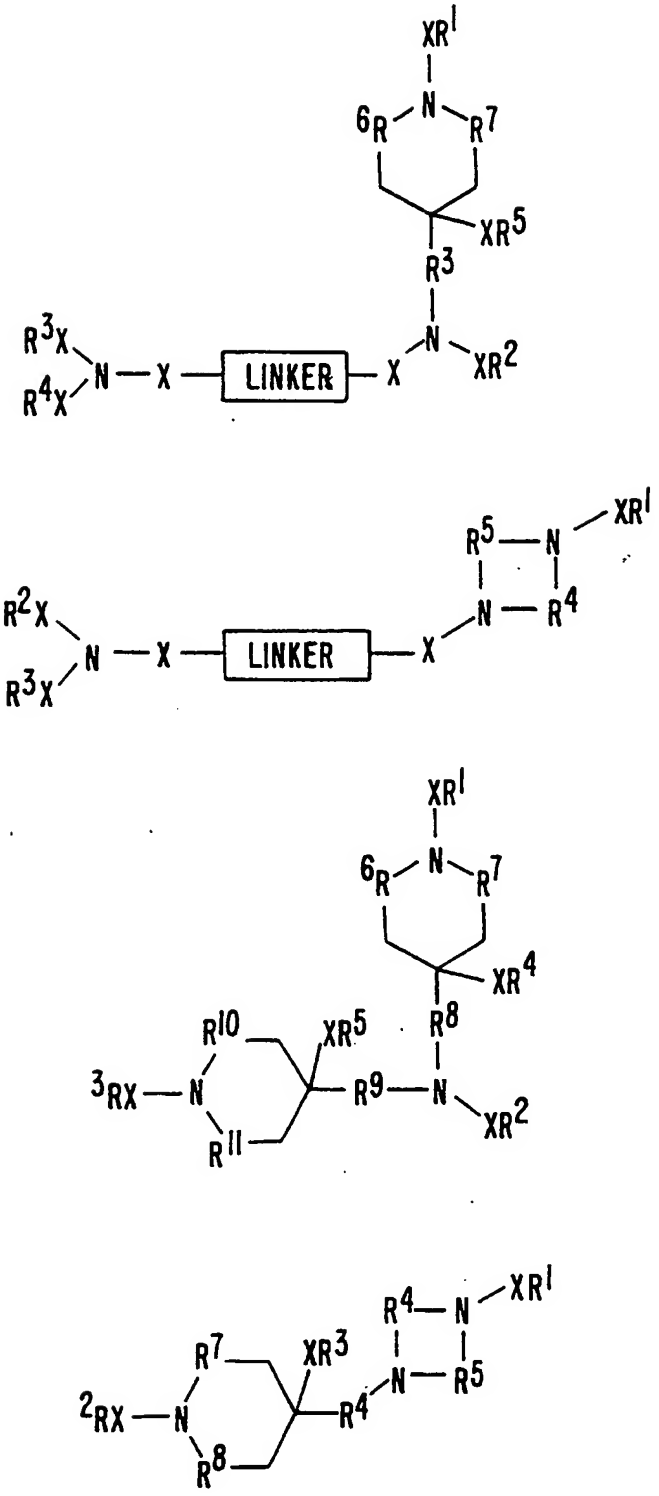

XR1
6R
N
R7
XR5
R3
R3X
R4X
N
X
LINKER
X
N
XR2
R5
N
XR1
R2X
R3X
N
X
LINKER
X
N
R4
XR1
6R
N
R7
XR4
R8
R10
XR5
3RX
N
R9
N
XR2
R11
R4
N
XR1
R7
XR3
2RX
N
R4
N
R5
R8

FIG. 1.

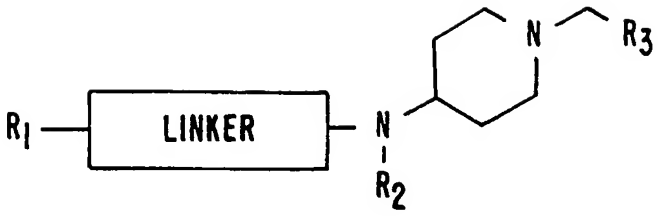
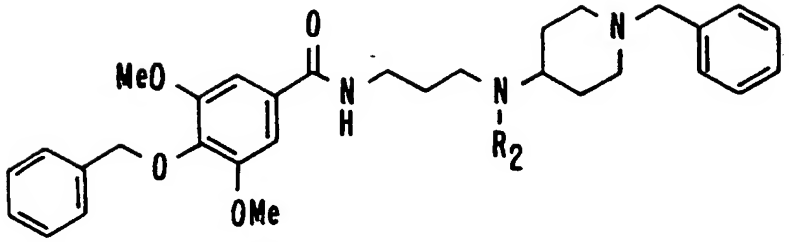


FIG. 2(a).



COMPOUND	R_2	M.W.
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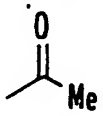
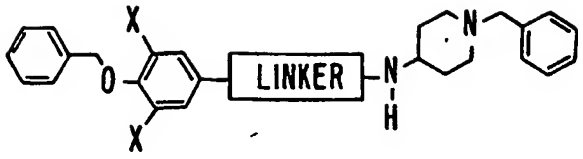
2	Me	532
3		560

FIG. 2(b).



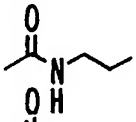
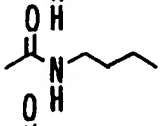
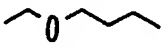
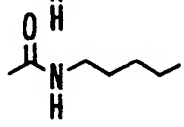
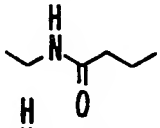
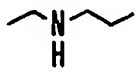
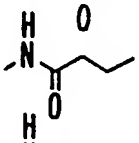
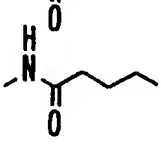
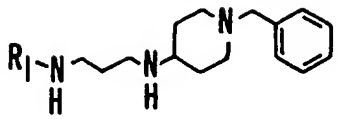
CMPD	X	LINKER	M.W.	CMPD	X	LINKER	M.W.
4	OMe		504	9	OMe		505
1	OMe		518	10	H		445
5	OMe		532	11	H		458
6	OMe		490	12	H		444
7	OMe		504	13	H		458
8	OMe		518				

FIG. 2(c).



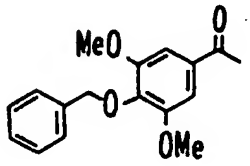
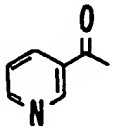
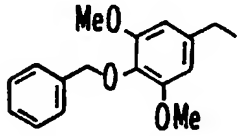
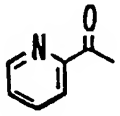
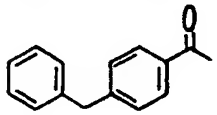
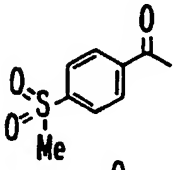
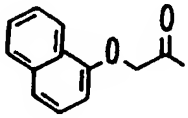
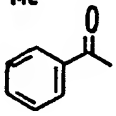
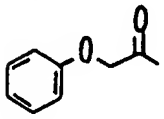
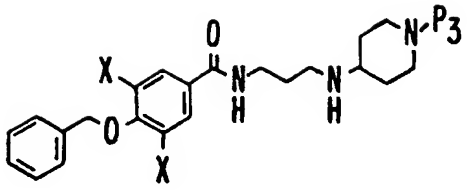
COMPD	R_1	M.W.	COMPD	R_1	M.W.
1		518	17		352
7		504	18		352
14		442	19		430
15		432	20		351
16		382	21	H	247

FIG. 2(d).



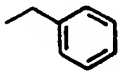
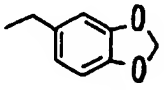
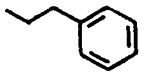
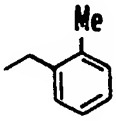
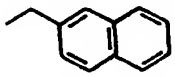
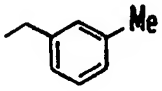
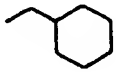
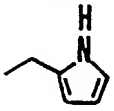
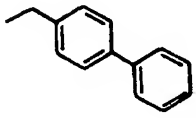
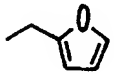
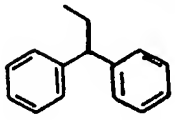
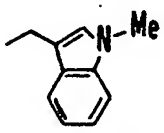
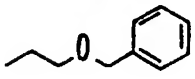
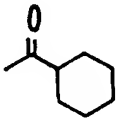
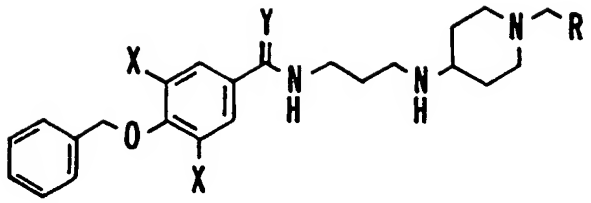
COMPD	R_3	X	M.W.	COMPD	R_3	X	M.W.
1		OMe	518	29		OMe	562
22		OMe	532	30		OMe	532
23		OMe	568	31		OMe	532
24		OMe	524	32		OMe	507
25		OMe	594	33		OMe	581
26		OMe	608	34	H	OMe	428
27		OMe	571	35	Me	OMe	442
28		OMe	562	36		H	478

FIG. 2(e).



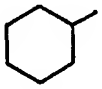
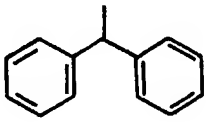
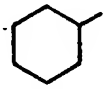
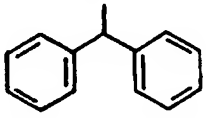
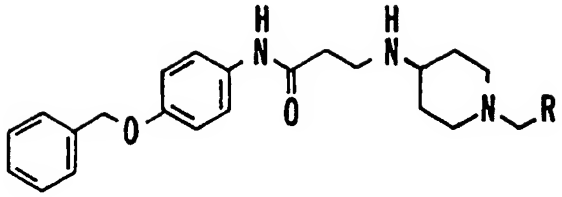
COMPD	X	Y	R	M.W.
37	H	O		464
38	H	O		548
39	OMe	H,H		510
40	OMe	H,H		594

FIG. 3(a).



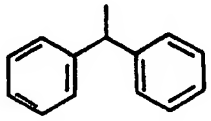
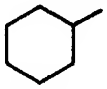
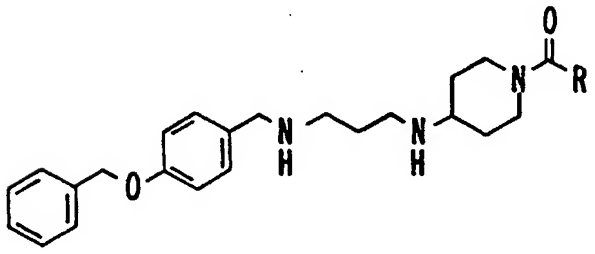
COMPD	R	M.W.
41		534
42		450

FIG. 3(b).



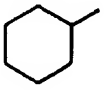
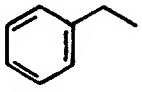
COMPD	R	M.W.
43		464
44		472

FIG. 3(c).

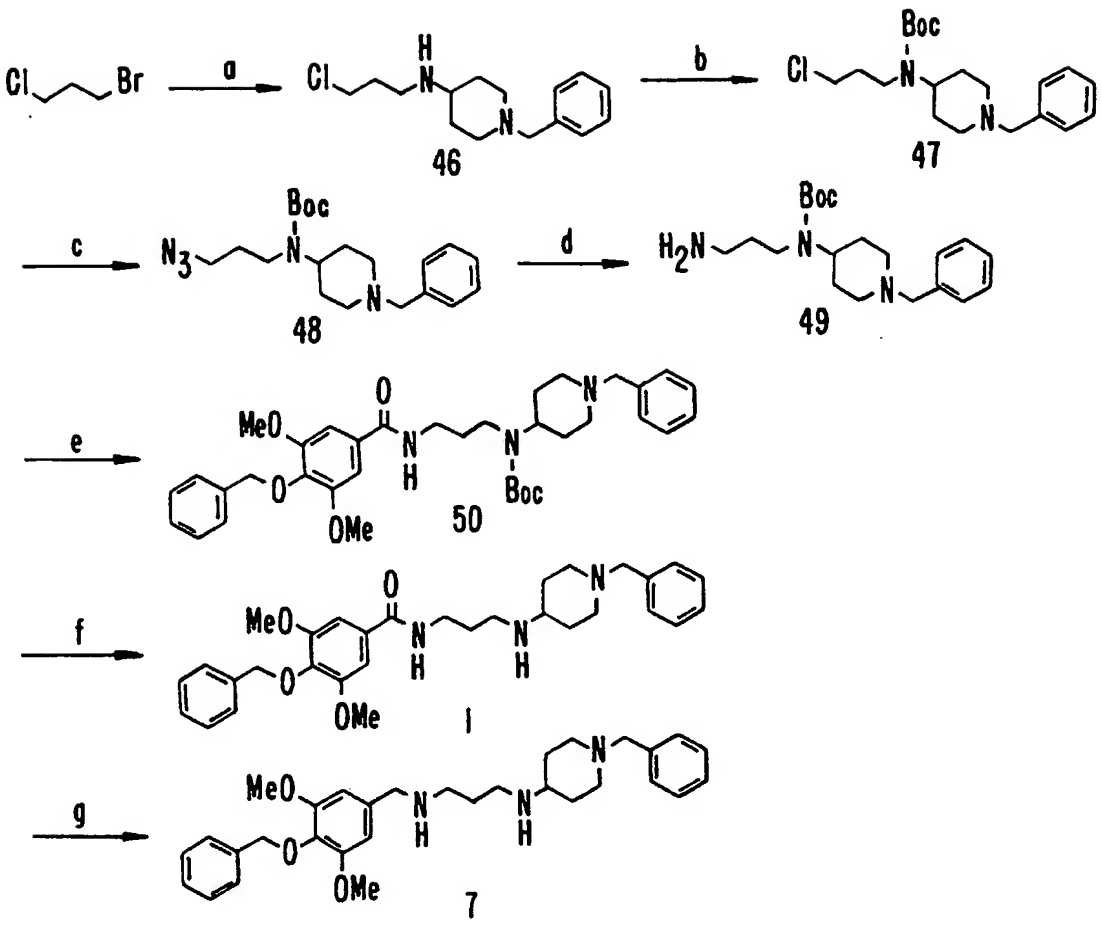

Cl
Br
a
H
N
Cl
N
46
b
Boc
N
Cl
N
47
c
Boc
N
N_3
N
48
d
Boc
N
H_2N
N
49
e
O
MeO
N
H
N
Boc
O
OMe
50
f
O
MeO
N
H
N
H
O
OMe
I
g
MeO
N
H
N
H
O
OMe
7

FIG. 4.

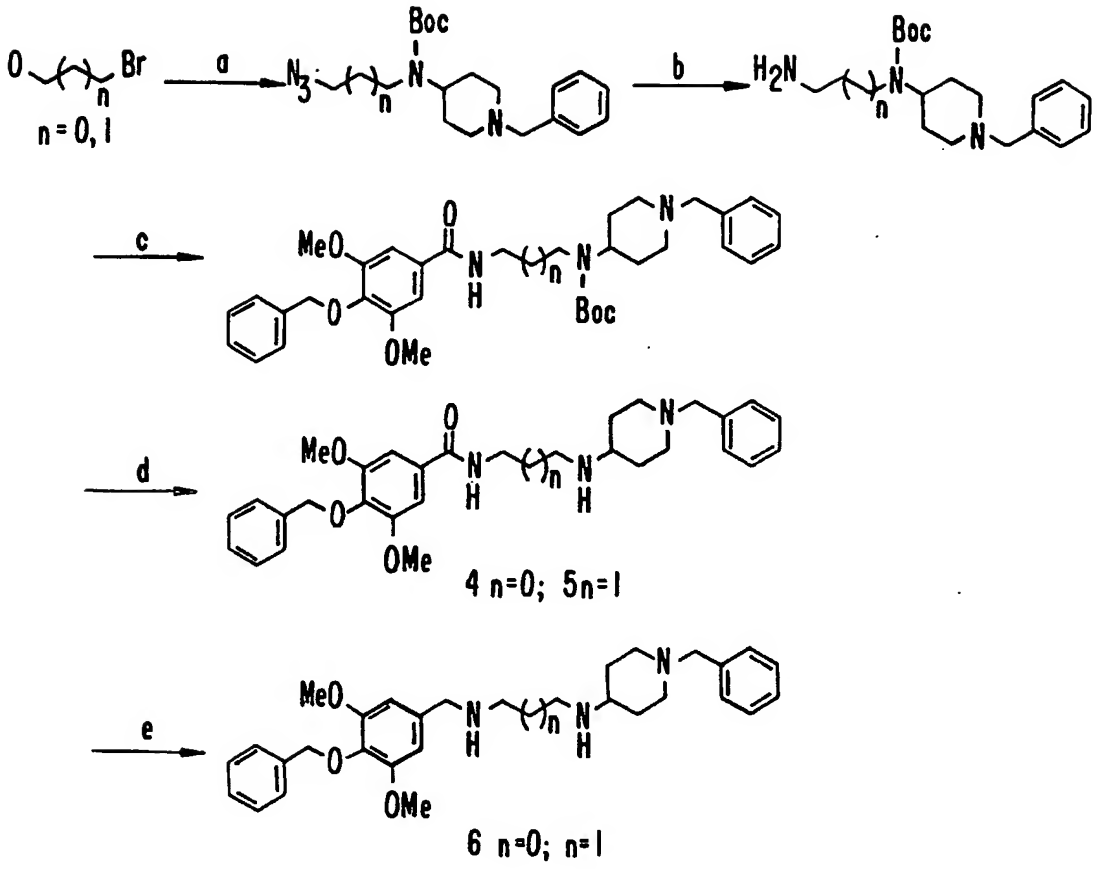


FIG. 5.

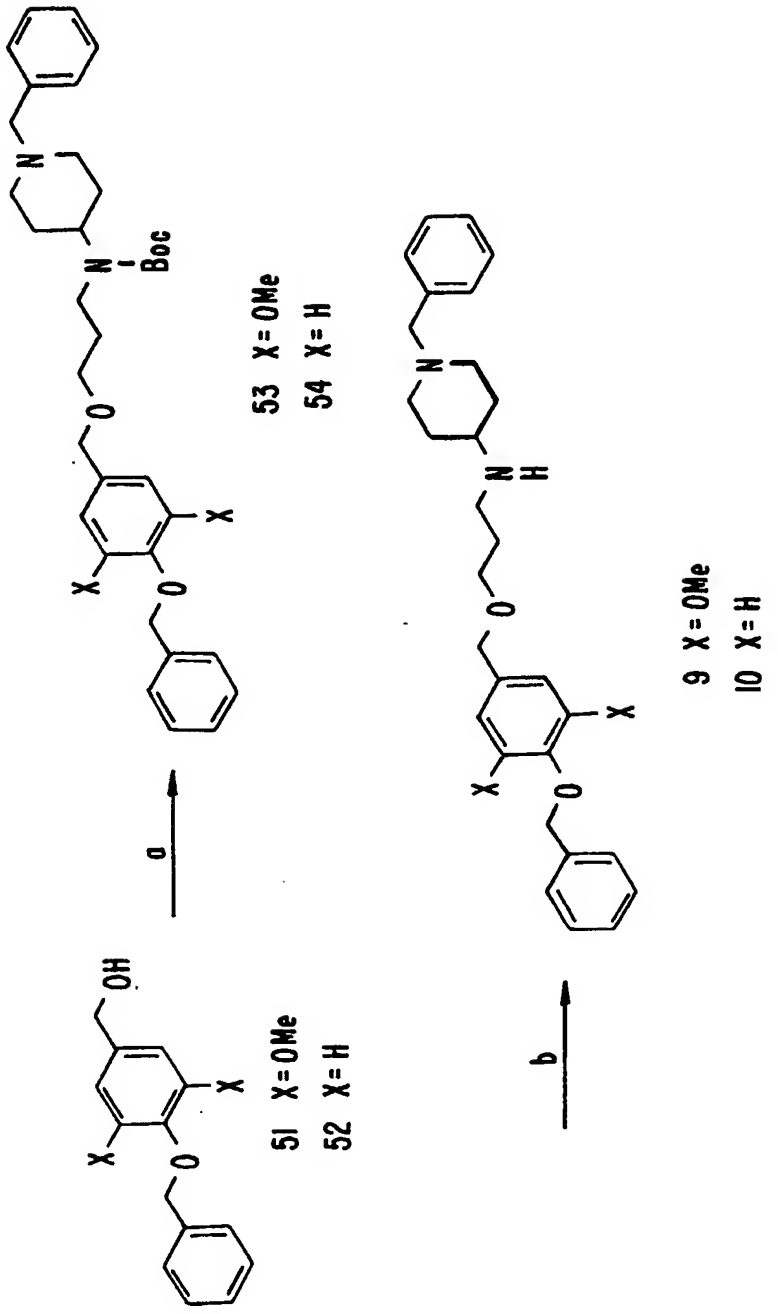


FIG. 6.

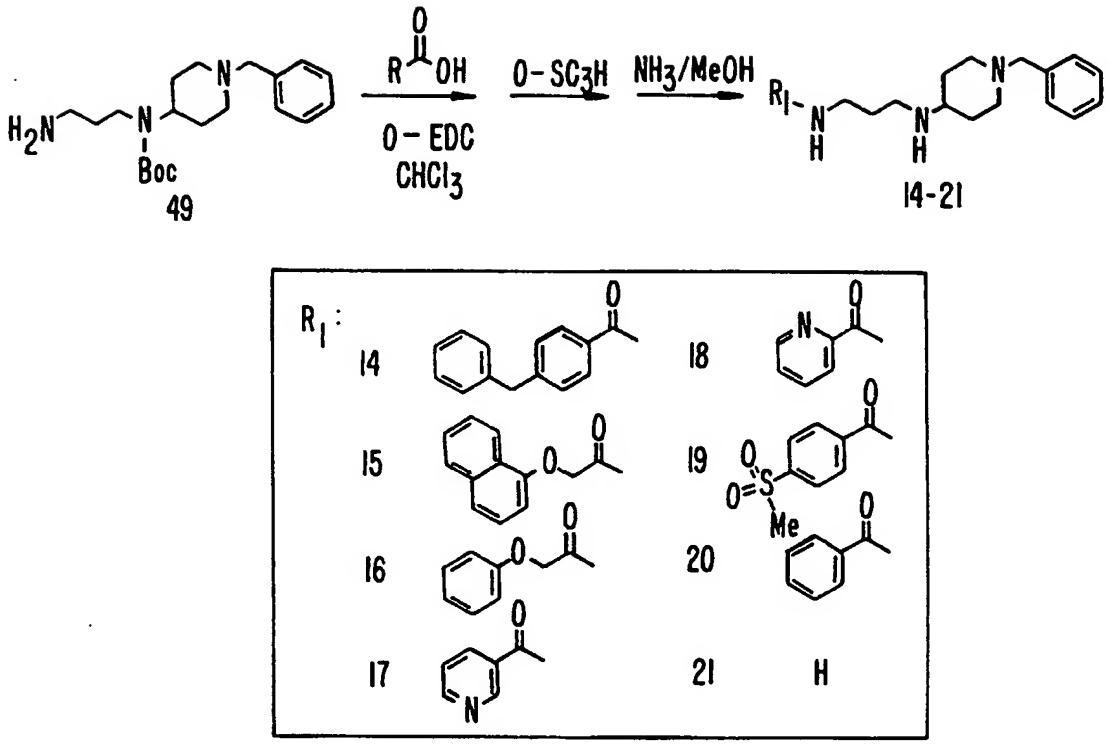

H2N
N
Boc
49
R OH
O-EDC
CHCl3
O-SC3H
NH3/MeOH
R1-NH
NH
14-21
R1:
14
15
16
17
18
19
20
21
H
O
N
S
Me

FIG. 7.

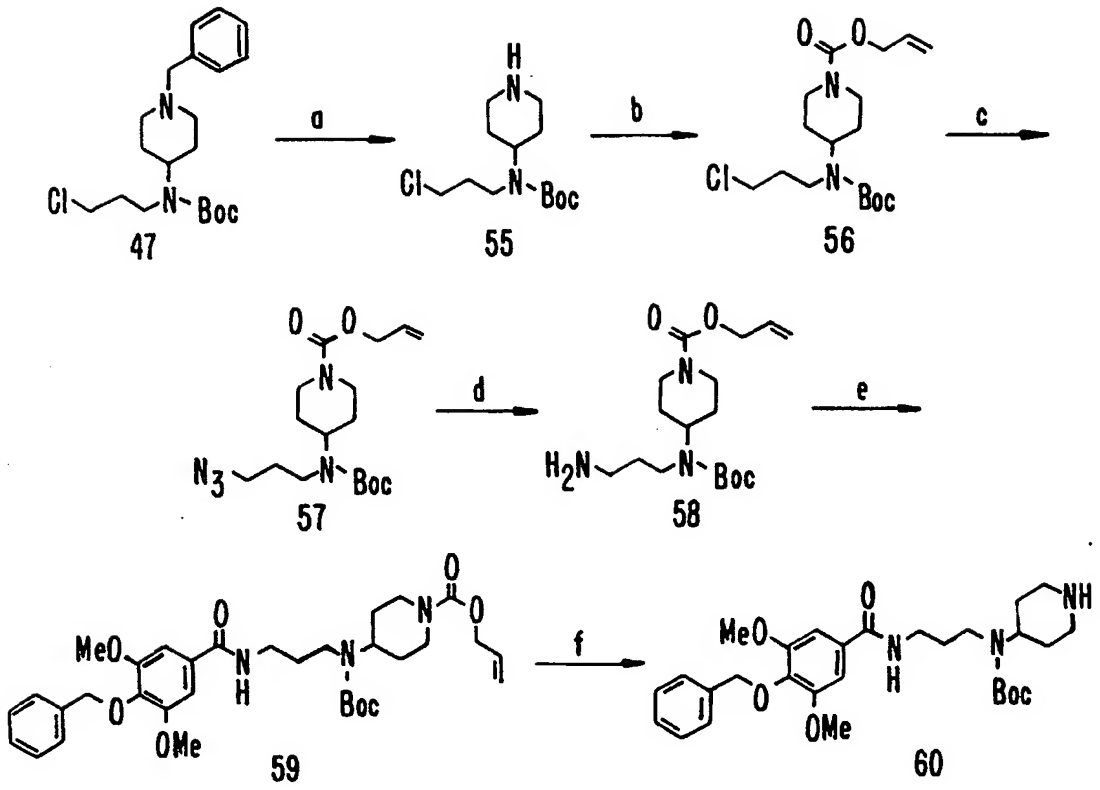


FIG. 8.

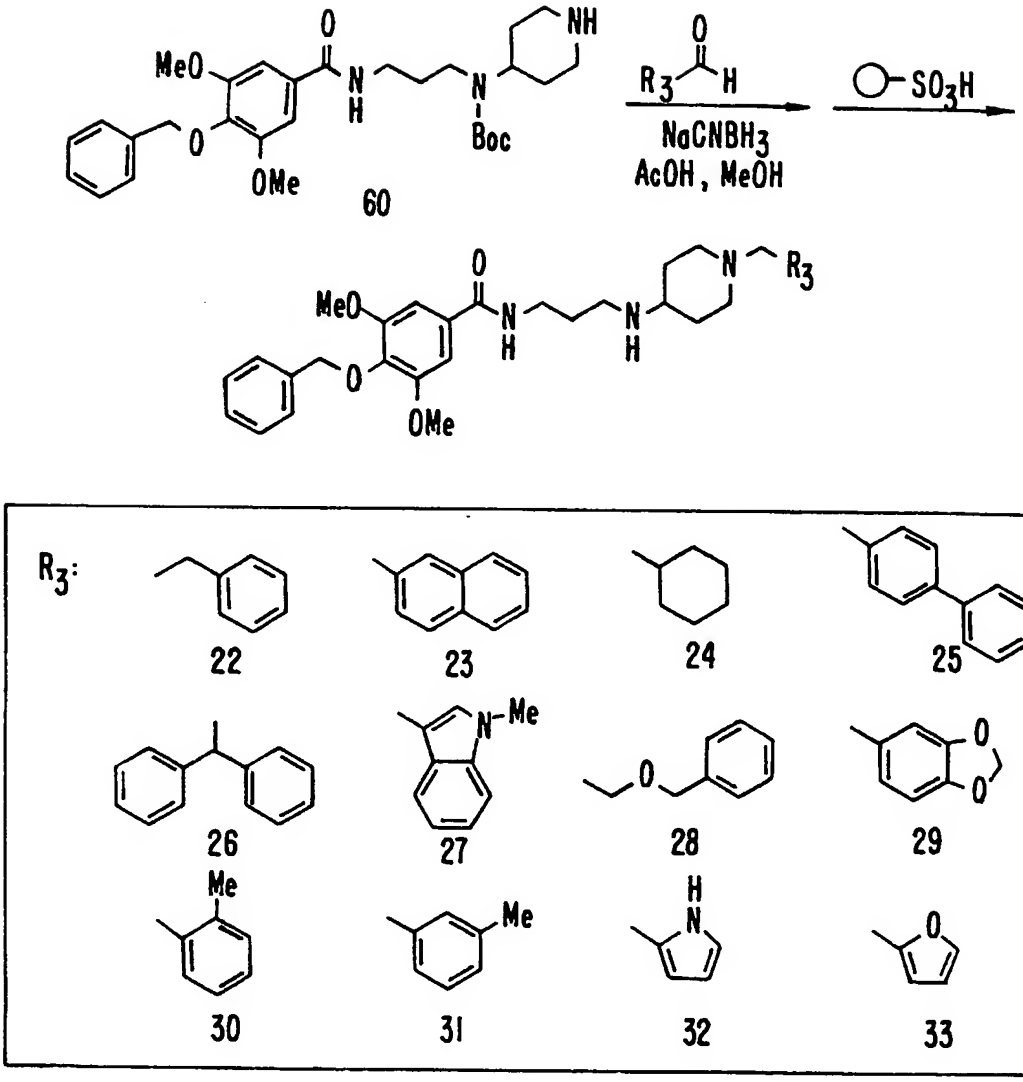

MeO
OMe
Boc
60
NaCNBH3
AcOH, MeOH
SO3H
R3:
22
23
24
25
26
27
28
29
30
31
32
33

FIG. 9.

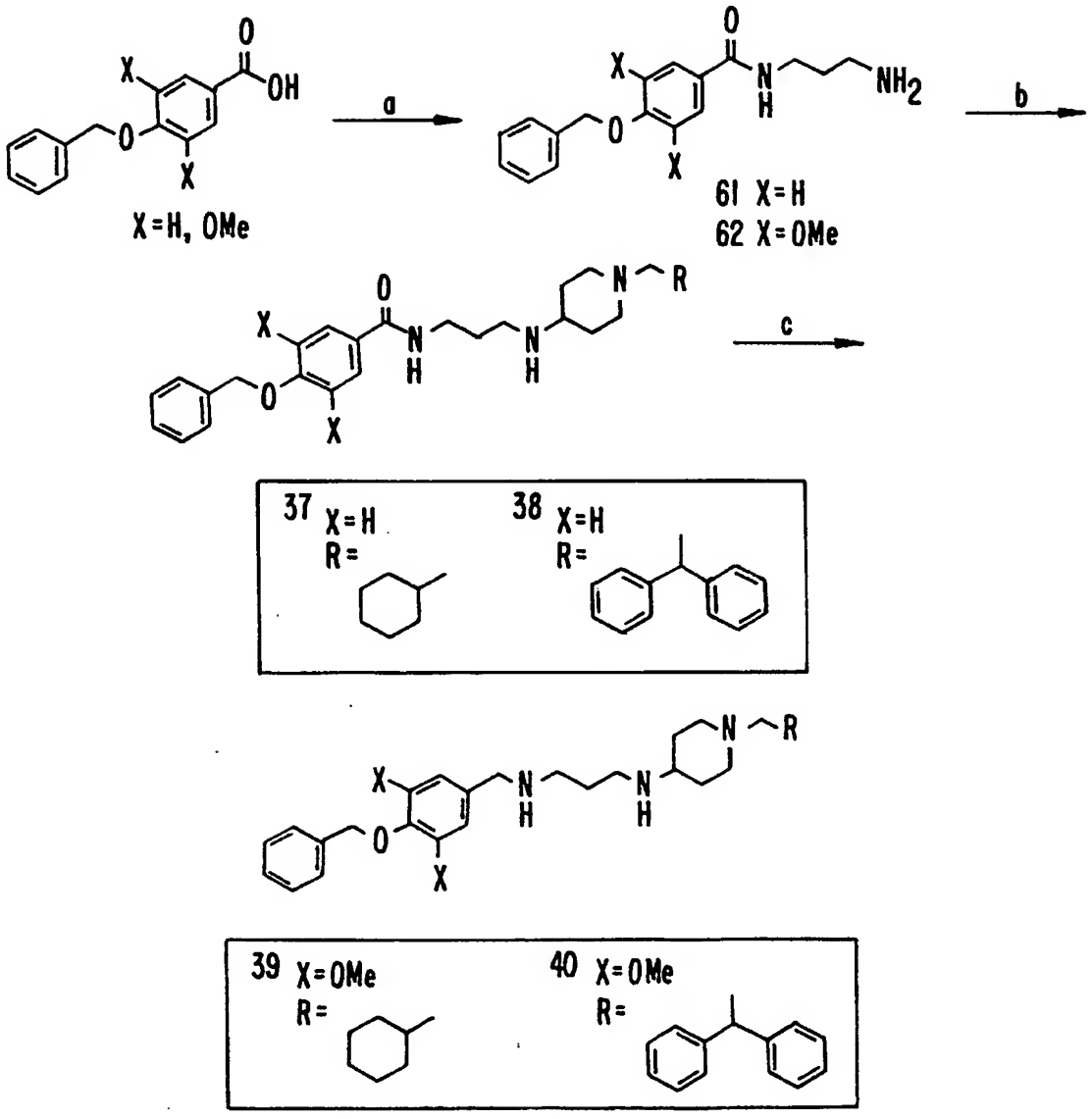


FIG. 10.

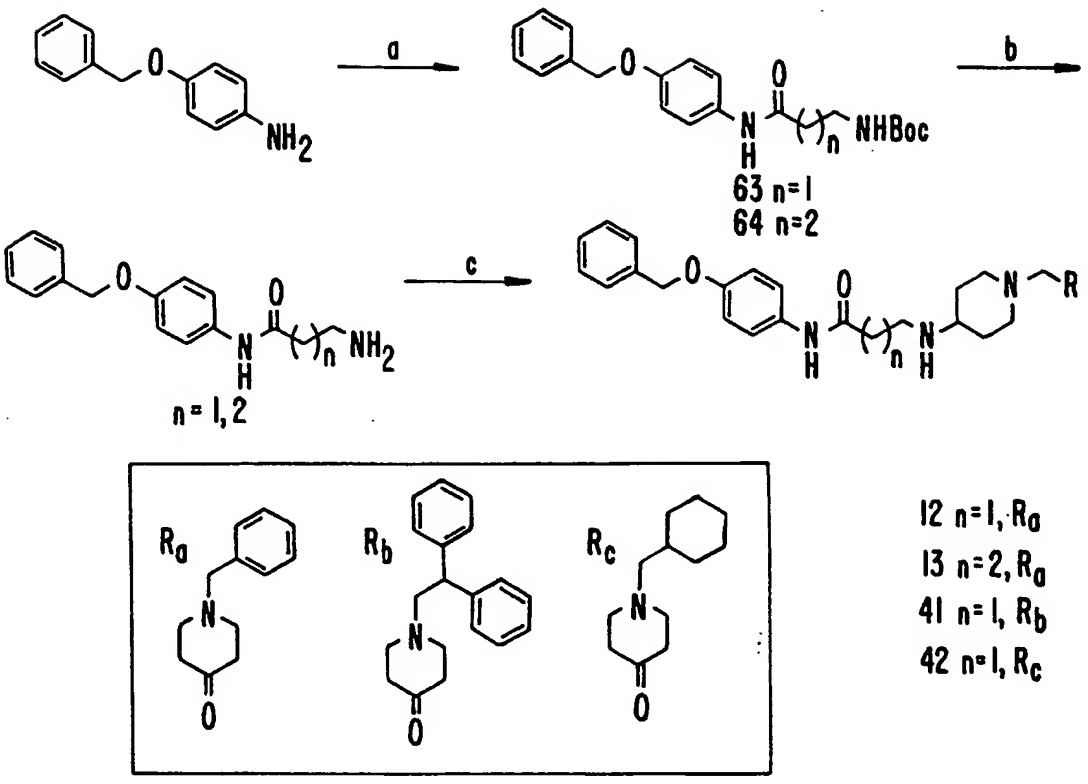

a
b
c
NH2
NHBoc
63 n=1
64 n=2
n=1,2
Ra
Rb
Rc
12 n=1, Ra
13 n=2, Ra
41 n=1, Rb
42 n=1, Rc

FIG. 11.

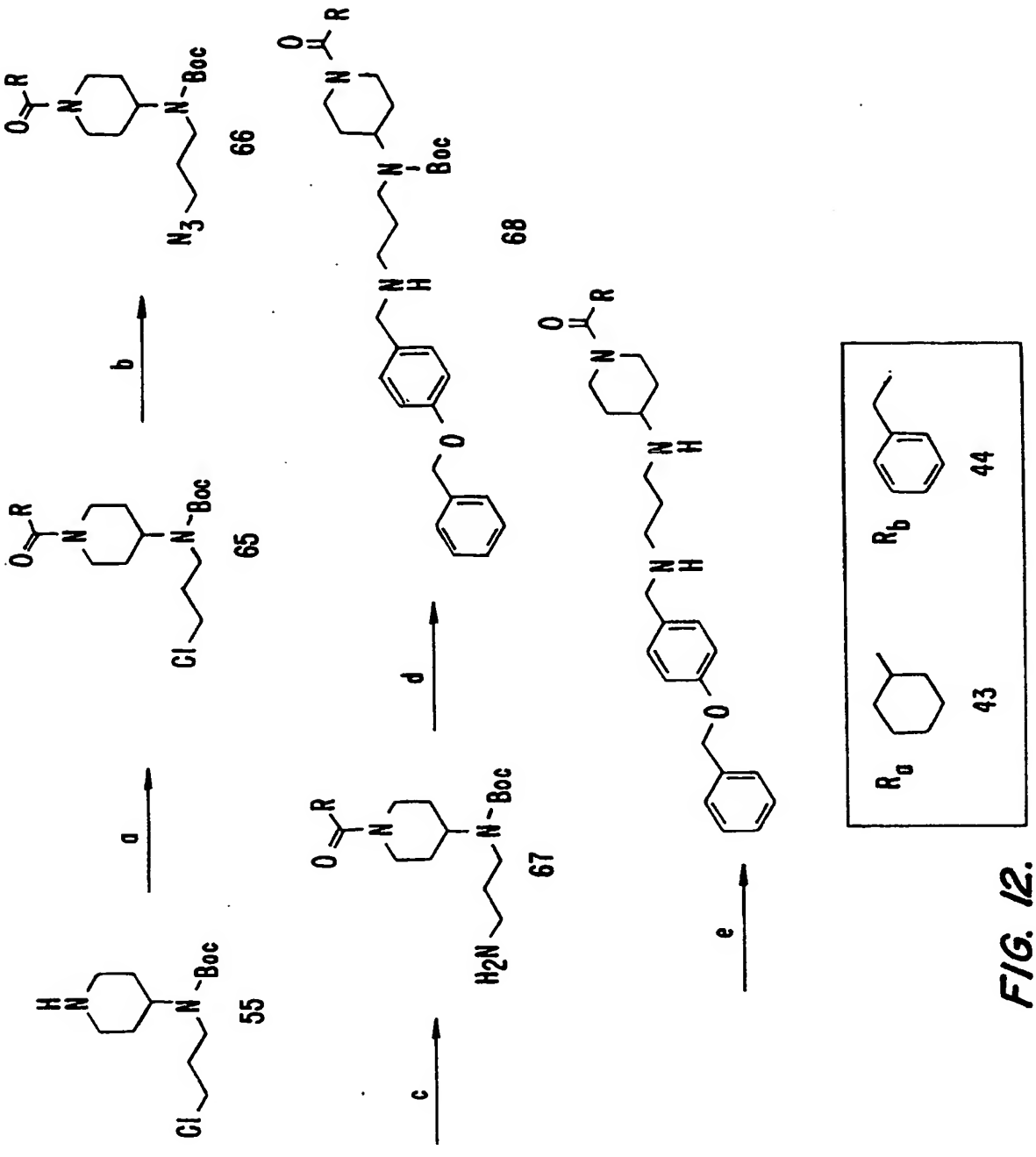


FIG. 12.

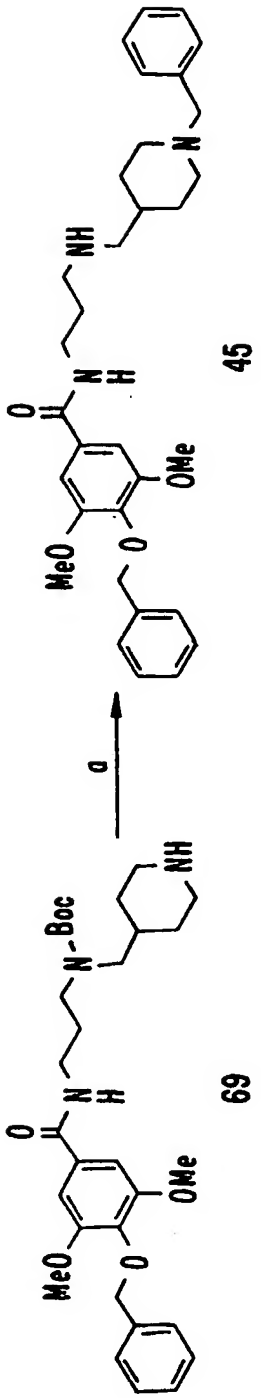


FIG. 13.

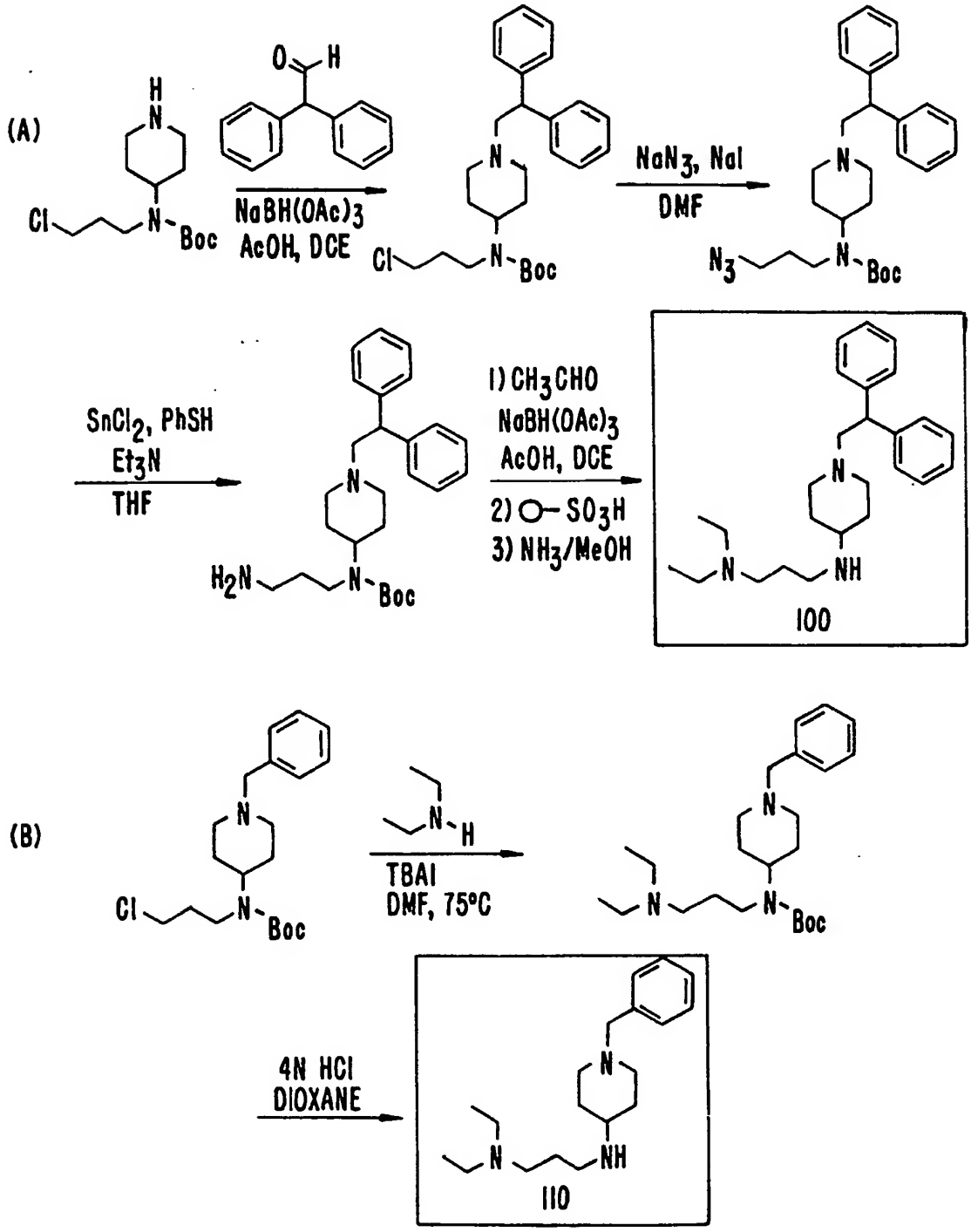

(A)
NaBH(OAc)3
AcOH, DCE
NaN3, NaI
DMF
SnCl2, PhSH
Et3N
THF
1) CH3CHO
NaBH(OAc)3
AcOH, DCE
2) O-SO3H
3) NH3/MeOH
100
(B)
TBAI
DMF, 75°C
4N HCl
DIOXANE
110

FIG. 14.

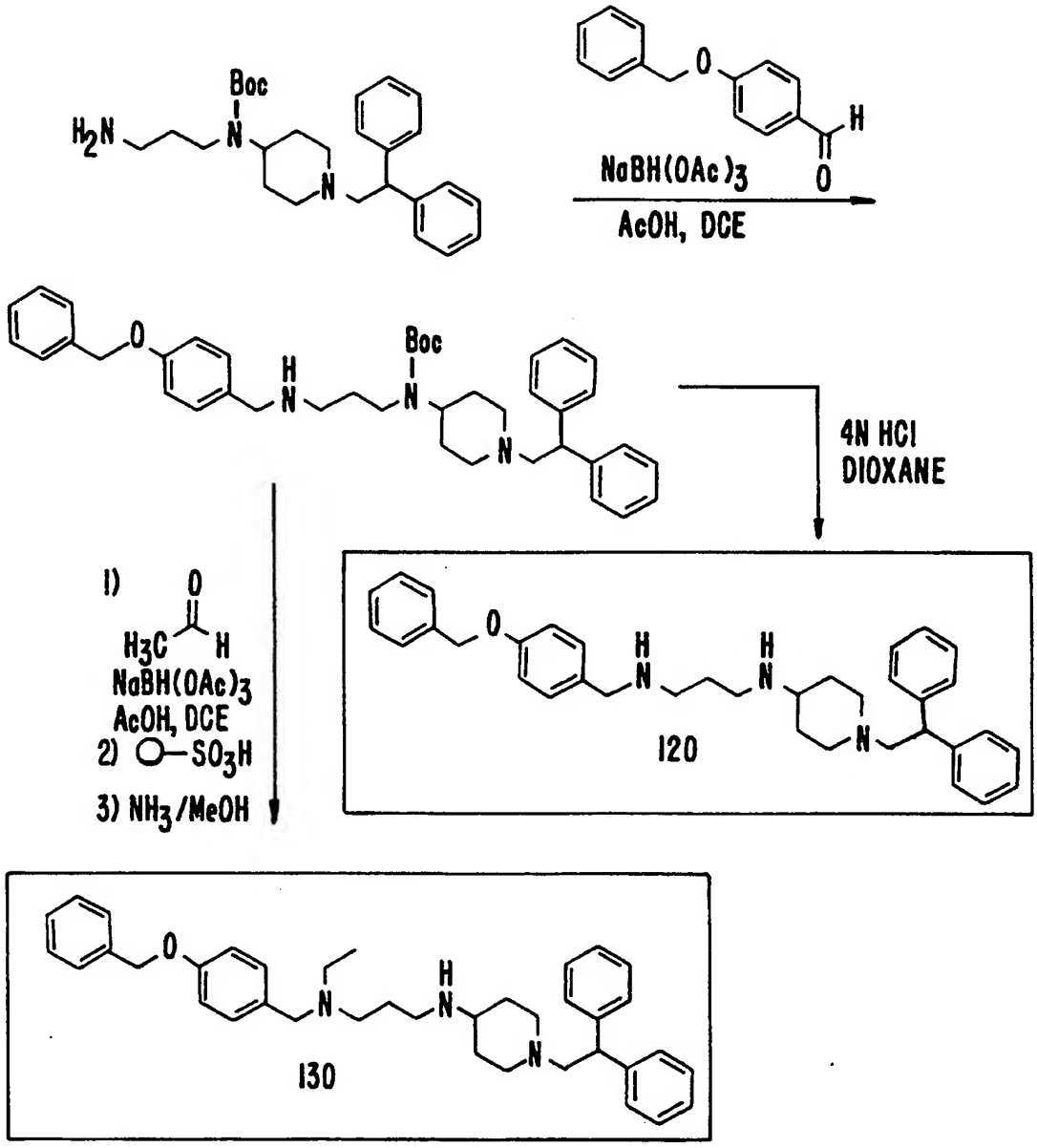

Boc
H_2N
N
N
O
H
O
$NaBH(OAc)_3$
AcOH, DCE
Boc
H
N
N
N
O
4N HCl
DIOXANE
1) O
H_3C H
$NaBH(OAc)_3$
AcOH, DCE
2) O—SO_3H
3) NH_3/MeOH
120
130

FIG. 15.

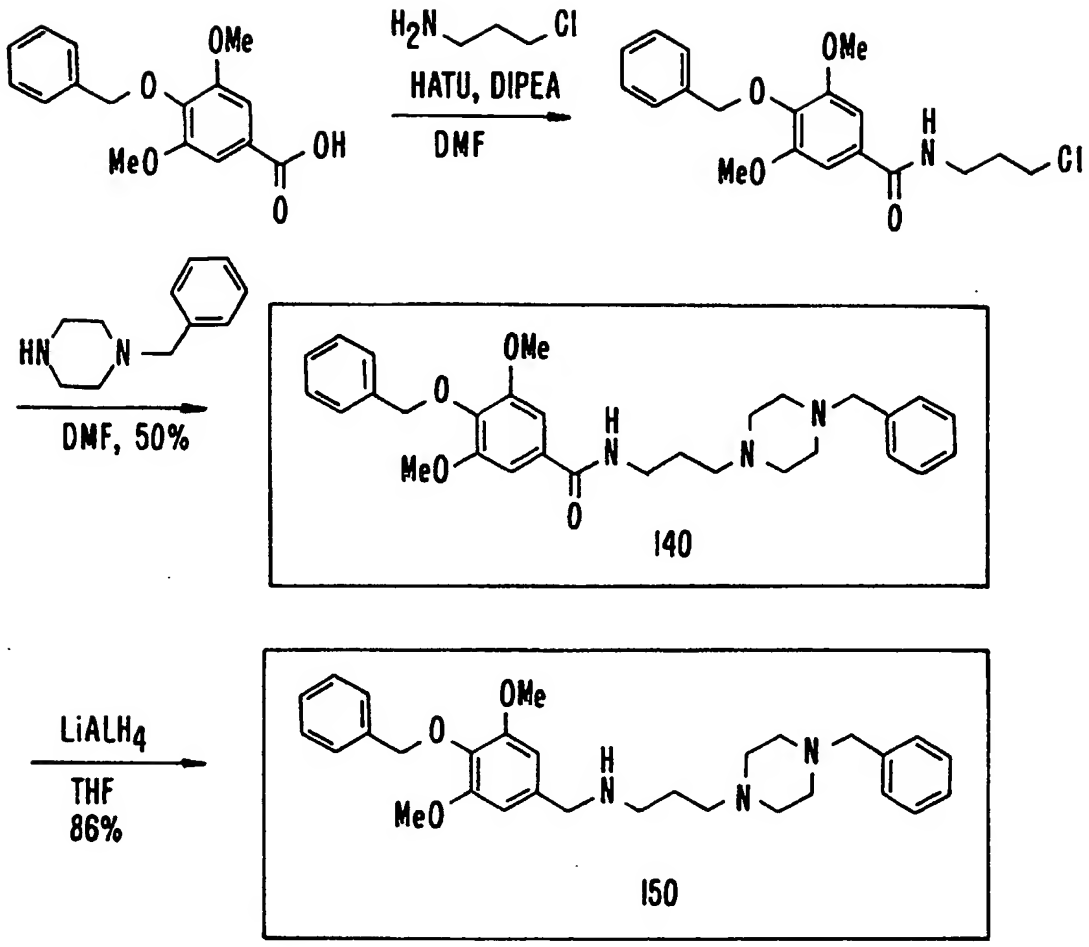

OMe
O
MeO
OH
O
H2N
Cl
HATU, DIPEA
DMF
OMe
O
MeO
H
N
Cl
O
HN
N
DMF, 50%
OMe
O
MeO
H
N
O
N
N
140
LiALH4
THF
86%
OMe
O
MeO
H
N
N
N
150

FIG. 16.

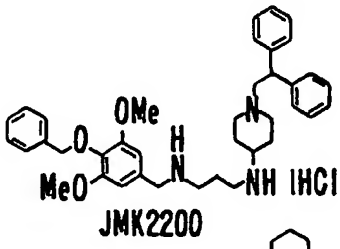
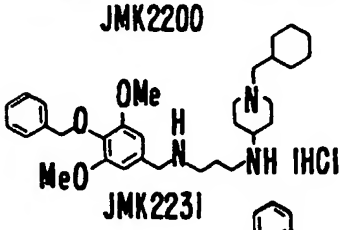
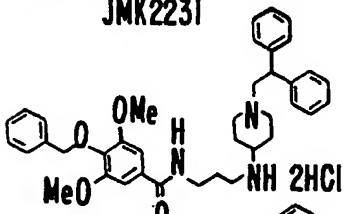
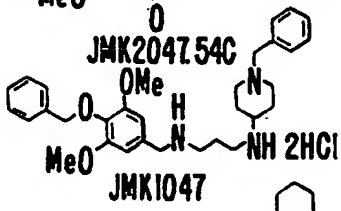
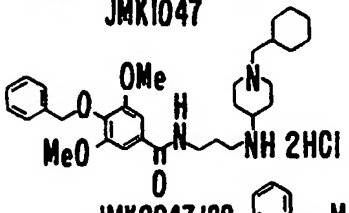
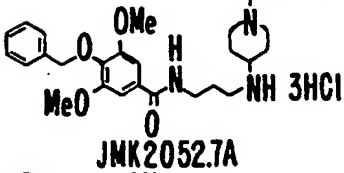
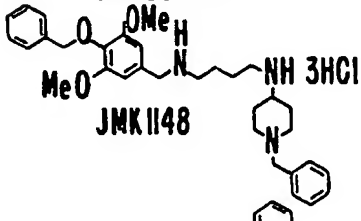
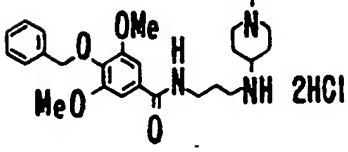
COMPD	STRUCTURE	M.W. HCl SALT/FREE AMINE
40	 JMK2200	703.19/593.31
39	 JMK2231	619.11/509.73
28	 JMK2047.54C	680.71/607.79
7	 JMK1047	613.07/503.69
24	 JMK2047.188	596.64/523.72
27	 JMK2052.7A	680.11/570.73
8	 JMK1148	827.09/517.71
22		804.61/531.89

FIG. 17A.

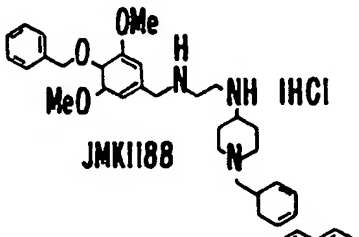
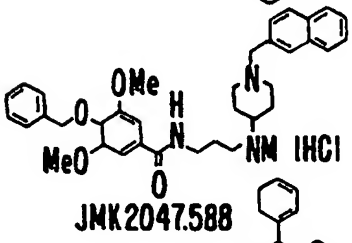
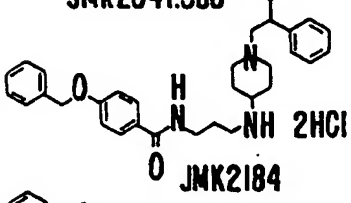
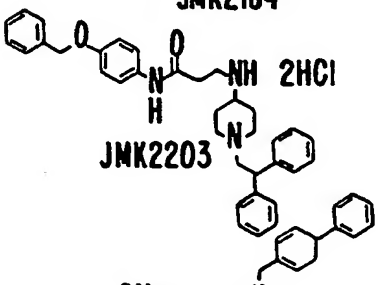
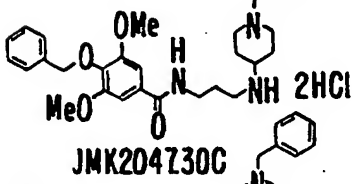
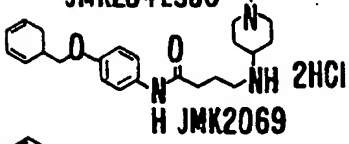
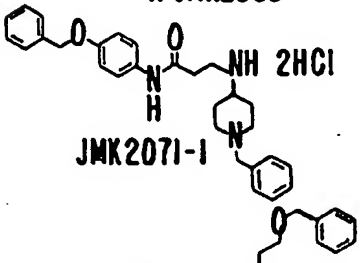
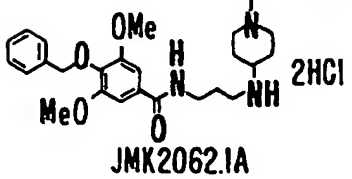
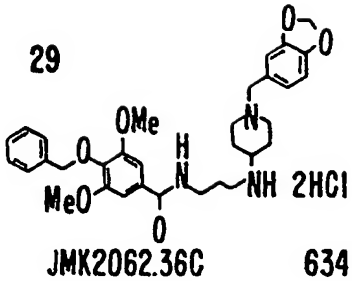
COMPD	STRUCTURE	M.W. HCl SALT/FREE AMINE
6	 JMK1188	699.04/489.66
23	 JMK2047.588	640.85/587.73
38	 JMK2184	620.66/547.74
41	 JMK2203	606.53/533.71
25	 JMK2047.30C	666.69/593.77
13	 H JMK2069	530.54/457.52
12	 JMK2071-1	516.51/443.59
28	 JMK2062.1A	634.54/561.72
29	 JMK2062.36C	634.60/561.58

FIG. 17B.

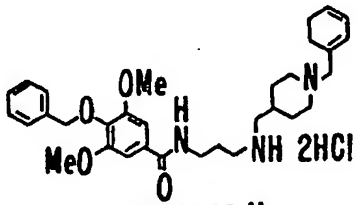
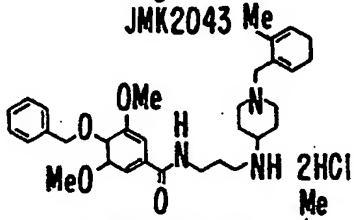
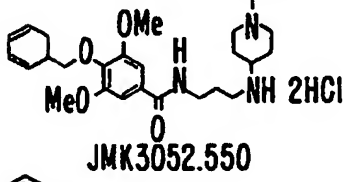
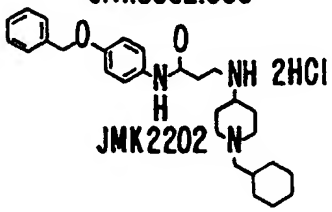
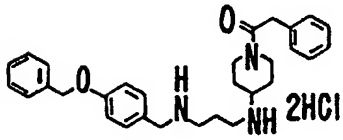
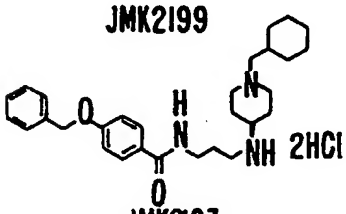
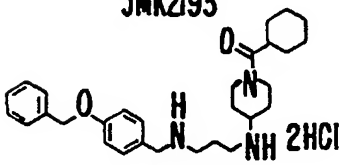
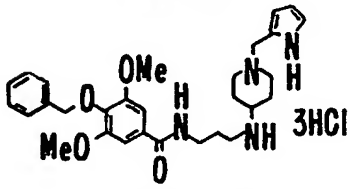
COMPD	STRUCTURE	M.W. HCl SALT/FREE AMINE
45	 JMK2043	504.61/531.69
30	 JMK3052.550	604.61/531.69
31	 JMK3052.550	604.61/531.69
42	 JMK2202	522.56/449.54
44	 JMK2199	544.56/471.54
37	 JMK2193	538.58/463.66
43	 JMK2199	536.58/463.66
32	 JMK2052.238	616.03/506.65

FIG. 17C.

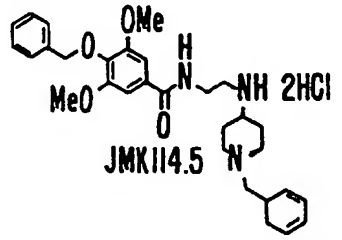
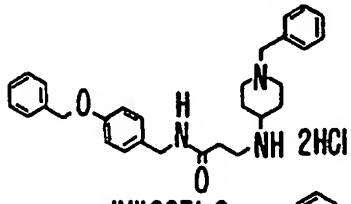
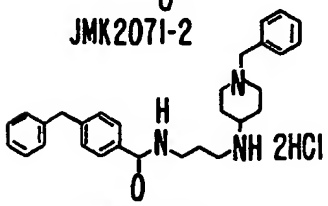
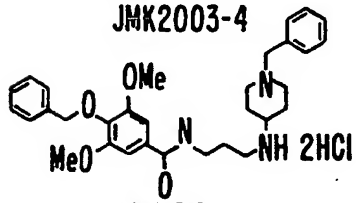
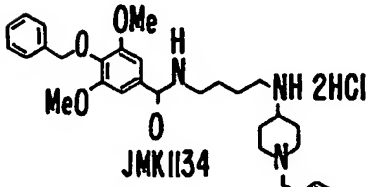
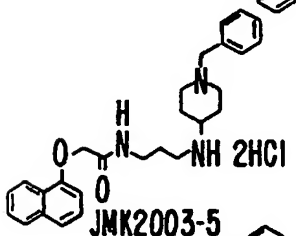
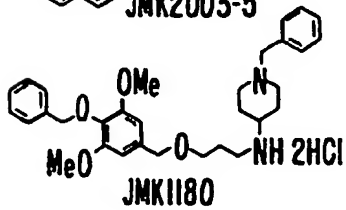
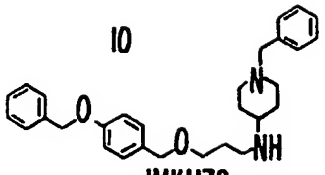
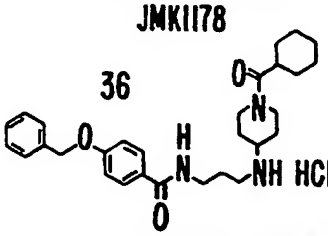
ENTRY	STRUCTURE	M.W. HCl SALT/FREE AMINE
4	 JMK1145	576.56/503.54
11	 JMK2071-2	530.54/457.52
14	 JMK2003-4	514.54/441.62
1	 JMK1017	590.59/517.67
5	 JMK1134	604.61/531.69
15	 JMK2003-5	504.50/431.58
9	 JMK1180	577.59/504.67
10	 JMK1178	444.52
36	 JMK2192	514.11/477.65

FIG. 17D.

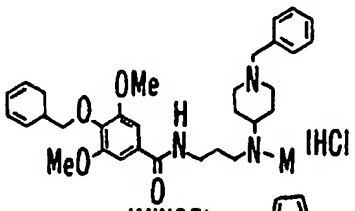
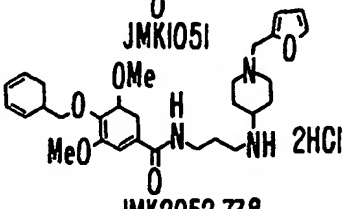
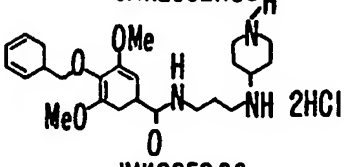
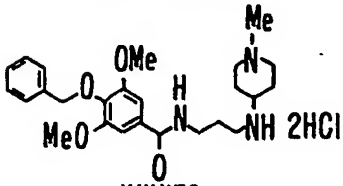
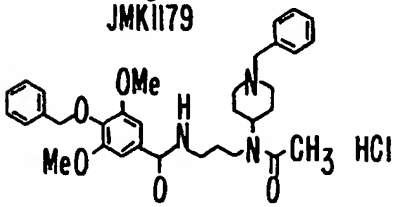
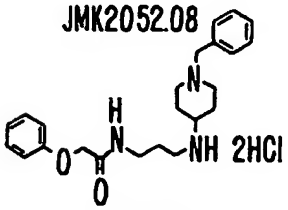
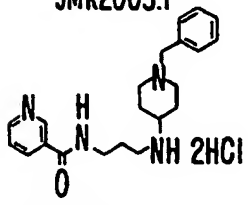
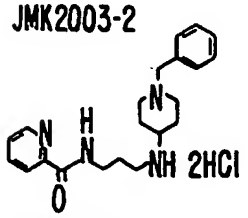
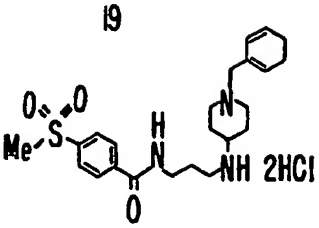
COMPD	STRUCTURE	M.W. HCl SALT/FREE AMINE
2	 JMK1051	604.61/531.69
33	 JMK2052.738	580.55/507.63
34	 JMK2052.08	500.46/427.54
35	 JMK1179	514.49/441.57
3	 JMK2052.08	596.16/559.70
16	 JMK2003.1	454.44/381.52
17	 JMK2003-2	461.36/352.48
18	 JMK2003-3	461.86/352.48
19	 JMK2003-4	502.50/429.58

FIG. 17E.

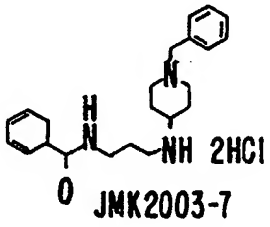
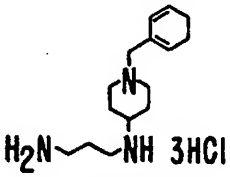
COMPD	STRUCTURE	M.W. HCl SALT/FREE AMINE
20	 JMK2003-7	424.41/351.49
21	 JMK1052	356.77/247.39

FIG. 17F.